Synthesis of fluorine-containing arylacetic acids via the Diels–Alder reaction of polyfluorinated cyclohexa-2,4-dienones with acetylenes

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Abstract

2,3,4,5,6-Pentafluoro-6-chloro-2,4-cyclohexadien-1-one (**I**) and 3-(pentafluorophenoxy)-6-chloro-2,4,5,6-tetrafluoro-2,4-cyclohexadien-1-one (**II**) readily undergo the Diels–Alder reaction with aryl- and alkyl-substituted acetylenes giving [2+4]-cycloadducts in good yield. The latter undergo aromatization by nucleophilic agents under mild conditions to α-chlorophenylacetic acid derivatives containing two or three fluorine atoms in the aromatic ring.

Introduction

Fluorine-containing (particularly polyfluorinated) cyclohexadienones are of considerable interest due to their high and varied reactivity stimulating the elaboration of new methods for the synthesis of fluoro-organic compounds. The properties of these compounds, such as ease of reduction and nucleophilic substitution, are well known and have already found use in synthesis [1]. In our study, we have used the ability of polyfluorinated cyclohexa-2,4-dienones to participate as dienes in the Diels–Alder reaction with substituted acetylenes. This is a new and promising route to fluoroaromatic compounds which are unavailable by other methods. Initially, we chose the most readily available polyfluorinated cyclohexa-2,4-dienones containing the geminal chlorine atom and a substituent in the 3-position. We have reported earlier [2] on the [2+4]-cycloaddition between 2,3,4,5,6-pentafluoro-6-chloro-2,4-cyclohexadien-1-one (**I**) and phenylacetylene.

The present work deals with the results of our studies on the reactions of 6-chloro-2,3,4,5,6-pentafluoro-2,4-cyclohexadien-1-one (**I**) and 6-chloro-3-(pentafluorophenoxy)-2,4,5,6-tetrafluoro-2,4-cyclohexadien-1-one (**II**) with substituted acetylenes, such as phenyl acetylene (**IIIa**), diphenyl acetylene (**IIIb**), 1-hexyne (**IIIc**), 3-hexyne (**IIId**), propargyl alcohol (**IIIe**) and 1,1-dimethylpropargyl alcohol (**IIIf**). The results obtained on reaction of the adducts formed with O- and N-nucleophiles are also presented.

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Experimental

The ^1H (200 MHz) and ^{19}F (188.28 MHz) NMR spectra were recorded on Bruker WP 200 SY or Bruker AC 200 spectrometers in CD_3COCD_3 or $CDCl_3$ as solvents (internal standards were TMS and C_6F_6, respectively). IR spectra of the neat liquids (films) and of the solids (KBr) were obtained using UR-20 or Specord M-80 spectrometers. MS spectra were recorded on MS-902 or Finnigan MAT 8200 instruments.

*Preparation of cycloadducts **IVa–f** and **Va–f**: general procedure*

A solution consisting of 6-chloro-2,3,4,5,6-pentafluoro-2,4-cyclohexadien-1-one (**I**) or 6-chloro-3-(pentafluorophenoxy)-2,4,5,6-tetrafluoro-2,4-cyclo-hexadien-1-one (**II**) (25–50 mmol) with equimolar amounts of acetylene **IIIa–f** in the corresponding solvent (25–50 ml) was refluxed and then evaporated. The residue was purified by crystallization or by distillation *in vacuo*, or by chromatography on silica gel. Table 1 presents the experimental and analytical data for the cycloadducts **IVa–f** and **Va–f** while Table 2 lists their spectral data.

*Preparation of the acids **VIa–f** and **VIIa–f**: general procedure*

A solution consisting of a 2.5-fold molar excess of NaOH in water (5–10 ml) was added dropwise (during 10–15 min) to a stirred solution of the cycloadduct (1–2 mmol) in dioxan (10–20 ml) at room temperature. The reaction mixture was stirred for a further 15 min, poured into 5% H_2SO_4 solution (25–50 ml) and extracted with diethyl ether. The extract was dried with $CaCl_2$ and evaporated. The residue was crystallized or sublimed. Table 3 presents experimental results and spectral data for the arylacetic acids **VIa–f** and **VIIa–f**.

*Preparation of methyl (**VIIIa, b, d–f; IXa**) and ethyl (**Xb–e; XIb, e**) esters: general procedure*

Anhydrous potassium carbonate (0.5–1.0 g) was added to a solution of the cycloadduct (1–2 mmol) in methanol (15–30 ml) or absolute ethanol (20–40 ml), and the mixture was stirred for 1 h at room temperature. It was then poured into 2% HCl solution and extracted with diethyl ether. The extract was dried over $CaCl_2$ and evaporated. The residue was crystallized or distilled *in vacuo* or sublimed. Table 4 presents the experimental results and spectral data for the arylacetic esters **VIII–XI** obtained.

*Preparation of amides **XIIa, b, d, f** and **XIIIa**: general procedure*

Aqueous ammonia (25% solution, 1–2 ml) was added dropwise to a stirred solution of the cycloadduct (1–2 mmol) in dioxan at room temperature. The reaction mixture was stirred for 30 min and then poured into water (50 ml) and extracted with diethyl ether. The extract was dried with $CaCl_2$ and evaporated. The residue was purified by crystallization.

TABLE 1

Experimental and analytical data for the cycloadducts **IV** and **V**

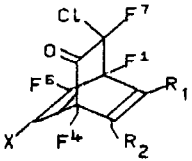
Cycloadduct	Solvent	Temp. (°C)	Time (h)	Yield (%)	M.p. (°C) or b.p. (°C/mmHg)	Found (%) (Calcd.) (%)					Empirical formula
						C	H	Cl	F	Mol. wt.[a]	
IVa	C_6H_6	80	4	92	114/5	51.95 (52.40)	1.88 (1.87)	11.05 (11.06)	29.98 (29.64)	320 (320.5)	$C_{14}H_6ClF_5O$
Va	C_6H_6	80	4	90	viscous liquid	49.22 (49.54)	1.30 (1.24)	7.13 (7.33)	35.46 (35.29)	485 (484.5)	$C_{20}H_6ClF_9O_2$
IVb	$C_6H_5CH_3$	110	30	86	108–109 (hexane)[b]	59.99 (60.53)	2.70 (2.52)	8.57 (8.95)	24.05 (23.96)	400 (396.5)	$C_{20}H_{10}ClF_5O$
Vb	$C_6H_5CH_3$	110	30	96	117–118 (hexane)[b]	55.47 (55.66)	1.50 (1.78)	6.61 (6.33)	29.94 (30.51)	555 (560.5)	$C_{26}H_{10}ClF_9O_2$
IVc	CCl_4	75	8	75	56/13	48.26 (47.92)	3.19 (3.33)	11.71 (11.81)	31.30 (31.61)	300 (300.5)	$C_{12}H_{10}ClF_5O$
Vc	CCl_4	75	8	91	37–39 (pentane)[b]	46.87 (46.50)	2.15 (2.15)	8.00 (7.64)	36.41 (36.81)	464 (464.5)	$C_{18}H_{10}ClF_9O_2$
IVd	CCl_4	75	30	76	91/6	48.23 (47.92)	3.30 (3.33)	11.84 (11.81)	31.24 (31.61)	302 (300.5)	$C_{12}H_{10}ClF_5O$
Vd	CCl_4	75	30	83	viscous liquid	46.52 (46.50)	2.11 (2.15)	7.82 (7.64)	36.55 (36.81)	462 (464.5)	$C_{18}H_{10}ClF_9O_2$
IVe	$C_6H_5CH_3$	110	6	84	glassy substance	39.34 (39.34)	1.30 (1.46)	13.36 (12.93)	34.19 (34.61)	278 (274.5)	$C_9H_4ClF_5O_2$
Ve	$C_6H_5CH_3$	110	6	73	glassy substance	41.26 (41.05)	1.09 (0.91)	8.19 (8.10)	40.09 (40.00)	436 (438.5)	$C_{15}H_4ClF_9O_3$
IVf	$C_6H_5CH_3$	110	8	79	glassy substance	43.19 (43.64)	2.61 (2.64)	12.08 (11.74)	31.33 (31.41)	307 (302.5)	$C_{11}H_8ClF_5O_2$
Vf	$C_6H_5CH_3$	110	8	81	glassy substance	43.90 (43.73)	1.72 (1.71)	7.43 (7.61)	36.36 (36.66)	469 (466.5)	$C_{17}H_8ClF_9O_3$

[a]Determined by vapour phase osmometry.

[b]Recrystallization solvent.

TABLE 2

Spectral data for cycloadducts **IV** and **V**

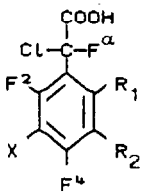


	^{19}F NMR spectra: chemical shifts (ppm) and *J* values (Hz)							^{1}H NMR spectra (ppm)	IR spectra (cm^{-1})	
	F^1	F^4	F^5 or			F^6	F^7		CX=CF	C=O
			F^o	F^m	F^p					
R_1=H, R_2=Ph; X=F^5 (**IVa**)	−41.0 (t, d) *10;2*	−39.2 (s)		13.4 (m)		7.5 (d, t) *6;3*	46.8 (d, d, d) *10;6:2*	6.90 (m, 1H, =CH); 7.44 (s, 5H, C_6H_5)	1750	1775
R_1=H, R_2=Ph; X=C_6F_5O (**Va**)	−39.4 (t) *10*	−35.4 (d) *6*	6.3	0.5	3.9	16.1 (s)	48.1 (d) *10*	7.06 (m, 1H, =CH); 7.46 (s, 5H, C_6H_5)	1725	1780
R_1=R_2=Ph; X=F^5 (**IVb**)	−36.9 (d) *10*	−37.0 (t) *4*		13.1 (d) *4*		10.0 (t) *6*	46.9 (d, d) *10;5*	7.12–7.44 (m, 10H, $2C_6H_5$)	1750	1775
R_1=R_2=Ph; X=C_6F_5O (**Vb**)	−35.6 (d) *11*	−33.6 (s)	7.6	1.8	5.1	17.3 (s)	47.5 (d) *11*	7.13–7.34 (m, 10H, 2 C_6H_5)	1725	1780
R_1=H, R_2=Bu^n; X=F^5 (**IVc**)	−40.6 (t) *8*	−43.8 (s)		13.3 (s)		7.2 (s)	47.6 (t) *8*	0.87 (t, 3H, CH_3); 1.21–1.53 (m, 4H, CH_2CH_2); 2.32 (t, 2H, CH_2); 6.23 (m, 1H, =CH)	1750	1780
R_1=H, R_2=Bu^n; X=C_6F_5O (**Vc**)	−40.0 (t) *9*	−41.2 (d) *5*	6.6	0.8	3.8	15.1 (s)	47.4 (d) *9*	0.88 (t, 3H, CH_3); 1.30–1.52 (m, 4H, CH_2CH_2); 2.35 (t, 2H, CH_2); 6.25 (m, 1H, =CH)	1720	1785
R_1=R_2=Et; X=F^5 (**IVd**)	−45.4 (d) *10*	−45.3 (s)		11.8 (s)		6.8 (s)	44.0 (d, d) *10;6*	1.02 (t, 3H, CH_3); 1.08 (t, 3H, CH_3); 2.29–2.47 (m, 4H, 2 CH_2)	1750	1775

$R_1=R_2=Et$;	−43.9	−41.8	6.5	0.8	4.0	14.6	45.2	1.02 (t, 3H, CH_3);	1720	1780
$X=C_6F_5O$ **(Vd)**	(d)	(s)				(s)	(d)	1.11 (t, 3H, CH_3);		
	10						*10*	2.31–2.50 (m, 4H, 2 CH_2)		
$R_1=H$, $R_2=CH_2OH$	−39.7	−46.4		12.7		7.5	48.8	2.07 (s, 2H, CH_2);	1760	1780
$X=F$[6] **(IVe)**	(t)	(s)		(s)		(s)	(t)	4.35 (s, 1H, OH);		
	8						*8*	6.72 (m, 1H, =CH)		
$R_1=H$, $R_2=CH_2OH$;	−39.2	−44.2	7.1	1.1	4.4	16.5	48.4	2.10 (s, 2H, CH_2);	1730	1785
$X=C_6F_5O$ **(Ve)**	(t)	(s)				(s)	(d)	4.44 (s, 1H, OH);		
	8						*8*	6.82 (m, 1H, =CH)		
$R_1=H$, $R_2=CMe_2OH$	−41.4	42.1		13.4		6.7	47.1	1.39 (s, 6H, 2 CH_3);	1755	1780
$X=F$[6] **(IVf)**	(t)	(s)		(s)		(s)	(d)	3.32 (s, 1H, OH);		
	10						*10*	6.48 (m, 1H, =CH)		
$R_1=H$, $R_2=CMe_2OH$;	−40.3	−38.9	6.7	0.8	4.2	15.7	47.4	1.40 (s, 6H, 2 CH_3);	1730	1785
$X=C_6F_5O$ **(Vf)**	(t)	(s)				(s)	(d)	3.48 (s, 1H, OH);		
	10						*10*	6.53 (m, 1H, =CH)		

TABLE 3

Experimental and spectral data for arylacetic acids **VI** and **VII**

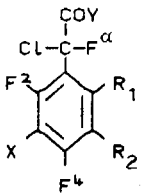
	Yield (%)	Melting point (°C)	Molecular weight Found (Calcd.)	Empirical formula
$R_1 = H$, $R_2 = Ph$; $X = F^3$ **(VIa)**	90	109–111 (benzene)[a]	318.0064 (318.0070)	$C_{14}H_7ClF_4O_2$
$R_1 = H$, $R_2 = Ph$; $X = C_6F_5O$ **(VIIa)**	93	glassy substance	481.9952 (481.9956)	$C_{20}H_7ClF_8O_3$
$R_1 = R_2 = Ph$; $X = F^3$ **(VIb)**	96	151–152 (benzene)	394.0378 (394.0384)	$C_{20}H_{11}ClF_4O_2$
$R_1 = R_2 = Ph$; $X = C_6F_5O$ **(VIIb)**	98	144–146 (benzene)	558.0215 (558.0269)	$C_{26}H_{11}ClF_8O_3$
$R_1 = H$, $R_2 = Bu^n$; $X = F^3$ **(VIc)**	98	glassy substance	298.0359 (298.0383)	$C_{12}H_{11}ClF_4O_2$
$R_1 = H$, $R_2 = Bu^n$; $X = C_6F_5O$ **(VIIc)**	95	glassy substance	462.0255 (462.0269)	$C_{18}H_{11}ClF_8O_3$
$R_1 = R_2 = Et$; $X = F^3$ **(VId)**	92	glassy substance	298.0359 (298.0383)	$C_{12}H_{11}ClF_4O_2$
$R_1 = R_2 = Et$; $X = C_6F_5O$ **(VIId)**	95	glassy substance	462.0255 (462.0269)	$C_{18}H_{11}ClF_8O_3$
$R_1 = H$, $R_2 = CH_2OH$; $X = F^3$ **(VIe)**	96	glassy substance	271.9851 (271.9863)	$C_9H_5ClF_4O_3$
$R_1 = H$, $R_2 = CH_2OH$; $X = C_6F_5O$ **(VIIe)**	94	123–124 (benzene)	435.9730 (435.9747)	$C_{15}H_9ClF_8O_4$
$R_1 = H$, $R_2 = CMe_2OH$; $X = F^3$ **(VIf)**	96	153–155 (benzene)	300.0163 (300.0176)	$C_{11}H_9ClF_4O_3$
$R_1 = H$, $R_2 = CMe_2OH$; $X = C_6F_5O$ **(VIIf)**	95	138–140 (benzene)	464.0050 (464.0061)	$C_{17}H_9ClF_8O_4$

[a]Recrystallization solvent.

^{19}F NMR spectra: chemical shifts (ppm) and J values (Hz)						^{1}H NMR spectra (ppm)
F^2	F^3 or			F^4	F^α	
	F^o	F^m	F^p			
28.9 (m) *20;10;9*		4.5 (t, d) *20;2*		29.9 (m) *20;9*	56.5 (d, d) *10;2*	7.32–7.48 (m, 5H, C_6H_5); 7.59 (m, 1H, CH arom.); 11.48 (s, 1H, COOH)
34.0 (m)	5.8	−0.2	1.4	35.8 (m)	57.0 (d) *10*	7.38–7.52 (m, 5H, C_6H_5); 7.71 (m, 1H, CH arom.); 11.28 (s, 1H, COOH)
32.4 (d, d, d) *20;10;8*		2.4 (d, d, d) *23;20;2*		33.0 (d, d) *23;10*	57.7 (d, d) *8;2*	7.04–7.23 (m, 10H, 2 C_6H_5); 10.24 (s, 1H, COOH)
38.0 (m)	6.0	−0.2	1.4	42.1 (m)	61.0 (d) *6*	6.82–7.10 (m, 10H, 2 C_6H_5); 10.44 (s, 1H, COOH)
25.2 (d, t) *19;9*		1.6 (d, d) *20;19*		26.7 (d, t) *20;9*	56.0 (d) *9*	0.92 (t, 3H, CH_3); 1.38 (m, 2H, CH_2); 1.55 (m, 2H, CH_2); 2.65 (t, 2H, CH_2); 7.36 (m, 1H, CH arom.); 12.06 (s, 1H, COOH)
29.8 (m)	5.2	−0.5	1.1	33.4 (m)	60.2 (d) *9*	0.89 (t, 3H, CH_3); 1.33 (m, 2H, CH_2); 1.51 (m, 2H, CH_2); 2.62 (t, 2H, CH_2); 7.30 (m, 1H, CH arom.); 12.02 (s, 1H, COOH)
28.1 (d, d) *21;10*		−0.5 (t) *21*		29.6 (d, d) *21;10*	53.7 (s)	1.12 (t, 3H, CH_3); 1.15 (t, 3H, CH_3); 2.65–2.92 (m, 4H, 2 CH_2); 10.86 (s, 1H, COOH)
31.7 (m) *10*	4.8	−1.2	0.3	35.8 (m) *10*	57.5 (s)	1.10 (t, 3H, CH_3); 1.13 (t, 3H, CH_3); 2.62–2.90 (m, 4H, 2 CH_2); 10.80 (s, 1H, COOH)
28.0 (m) *20;10*		3.4 (t) *20*		29.4 (m) *20;10*	58.0 (d) *10*	3.80 (s, 2H, CH_2); 4.62 (s, 1H, OH); 7.03 (m, 1H, CH arom.); 8.53 (s, 1H, COOH)
32.2 (m)	5.7	−0.3	1.2	36.0 (m)	61.9 (d) *10*	3.77 (s, 2H, CH_2); 4.60 (s, 1H, OH); 7.00 (s, 1H, CH arom.); 8.47 (s, 1H, COOH)
28.0 (m) *20;9*		3.4 (t) *20*		33.4 (m) *20;9*	59.6 (d) *9*	1.60 (s, 6H, 2 CH_3); 8.05 (m, 1H, CH arom.); OH and COOH not observed
32.1 (m)	5.8	−0.2	1.2	37.8 (m)	62.3 (d) *10*	1.59 (s, 6H, 2 CH_3); 8.04 (m, 1H, CH arom.); OH and COOH not observed

TABLE 4

Experimental and spectral data for arylacetic esters **VIII–XI**

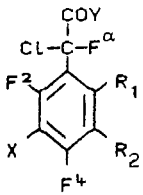
	Yield (%)	M.p. (°C) or b.p. (°C/mmHg)	Molecular weight Found (Calcd.)	Empirical formula
R_1 = H, R_2 = Ph; X = F^3; Y = OMe (**VIIIa**)	90	viscous liquid	332.0218 (332.0227)	$C_{15}H_9ClF_4O_2$
R_1 = H, R_2 = Ph; X = C_6F_5O; Y = OMe (**IXa**)	76	glassy substance	496.0092 (496.0112)	$C_{21}H_9ClF_8O_3$
R_1 = R_2 = Ph; X = F^3; Y = OMe (**VIIIb**)	97	149–151 (CCl_4)[a]	408.0538 (408.0540)	$C_{21}H_{13}ClF_4O_2$
R_1 = R_2 = Ph; X = F^3; Y = OEt (**Xb**)	93	123–124 (CCl_4)	422.0692 (422.0696)	$C_{22}H_{15}ClF_4O_2$
R_1 = R_2 = Ph; X = C_6F_5O; Y = OEt (**XIb**)	68	147–150 (CCl_4)	586.0573 (586.0582)	$C_{28}H_{15}ClF_8O_3$
R_1 = H, R_2 = Bu^n; X = F^3; Y = OEt (**Xc**)	73	viscous liquid	326.0677 (326.0696)	$C_{14}H_{15}ClF_4O_2$
R_1 = R_2 = Et; X = F^3; Y = OMe (**VIIId**)	77	viscous liquid	312.0533 (312.0540)	$C_{13}H_{13}ClF_4O_2$
R_1 = R_2 = Et; X = F^3; Y = OEt (**Xd**)	74	viscous liquid	326.0677 (326.0696)	$C_{14}H_{15}ClF_4O_2$
R_1 = H, R_2 = CH_2OH; X = F^3; Y = OMe (**VIIIe**)	73	157/5	286.0015 (286.0020)	$C_{10}H_7ClF_4O_3$
R_1 = H, R_2 = CH_2OH; X = F^3; Y = OEt (**Xe**)	65	viscous liquid	300.0163 (300.0176)	$C_{11}H_9ClF_4O_3$
R_1 = H, R_2 = CH_2OH; X = C_6F_5O; Y = OEt (**XIe**)	70	glassy substance	464.0050 (464.0061)	$C_{17}H_9ClF_8O_4$
R_1 = H, R_2 = CMe_2OH; X = F^3; Y = OMe (**VIIIf**)	83	glassy substance	314.0327 (314.0333)	$C_{12}H_{11}ClF_4O_3$

[a]Recrystallization solvent.

^{19}F NMR spectra: chemical shifts (ppm) and J values (Hz)						^{1}H NMR spectra (ppm)
F^2	F^3 or			F^4	F^α	
	F^o	F^m	F^p			
28.6 (m) *20;10;8*		4.6 (t, d) *20;2*		29.2 (m) *20;8*	57.0 (d, d) *10;2*	3.94 (s, 3H, CH_3); 7.42–7.53 (m, 5H, C_6H_5); 7.65 (m, 1H, CH arom.)
34.5 (m)	5.8	−0.3	1.4	35.8 (m)	57.2 (d) *10*	4.03 (s, 3H, CH_3); 7.40–7.51 (m, 5H, C_6H_5); 7.74 (m, 1H, CH arom.)
31.2 (m) *20;10;8*		3.2 (m) *23;20;3*		32.8 (d, d) *23;10*	57.3 (d, d) *8;3*	3.71 (s, 3H, CH_3); 7.00–7.19 (m, 10H, 2 C_6H_5)
31.7 (m) *20;10;8*		2.7 (m) *23;20;3*		32.9 (d, d) *23;10*	58.6 (d, d) *8;3*	1.28 (t, 3H, CH_3); 4.15 (q, 2H, CH_2); 6.86–7.29 (m, 10H, 2 C_6H_5)
38.1 (m)	6.1	−0.2	1.3	41.8 (m)	61.1 (d) *7*	1.31 (t, 3H, CH_3); 4.11 (q, 2H, CH_2); 6.78–7.13 (m, 10H, 2 C_6H_5)
27.2 (t, d) *20;10*		3.6 (t) *20*		28.6 (t, d) *20;10*	58.0 (d) *10*	0.95 (t, 3H, CH_3); 1.27 (t, 3H, CH_3); 1.41 (m, 2H, CH_2); 1.59 (m, 2H, CH_2); 2.69 (t, 2H, CH_2); 4.20 (q, 2H, CH_2); 7.38 (t, 1H, CH arom.)
28.0 (d, d) *21;10*		−0.6 (t, d) *21;2*		28.5 (d, d) *21;10*	55.3 (s)	1.14 (t, 3H, CH_3); 1.17 (t, 3H, CH_3); 2.70–2.96 (m, 4H, 2 CH_2); 3.91 (s, 3H, CH_3)
28.1 (d, d) *21;10*		−0.6 (t, d) *21;2*		28.8 (d, d) *21;10*	54.6 (s)	1.18 (t, 6H, 2 CH_3); 1.33 (t, 3H, CH_3); 2.71–2.96 (m, 4H, 2 CH_2); 4.34 (q, 2H, CH_2)
26.8 (m) *20;10*		3.6 (t) *20*		28.5 (m) *20;10*	55.3 (d) *10*	3.70 (s, 1H, OH); 3.97 (s, 3H, CH_3); 4.73 (s, 2H, CH_2); 7.71 (m, 1H, CH arom.)
27.5 (m) *20;10*		3.5 (t) *20*		29.0 (m) *20;10*	56.6 (d) *10*	1.31 (t, 3H, CH_3); 3.95 (s, 1H, OH); 4.34 (q, 2H, CH_2); 4.73 (s, 2H, CH_2); 7.63 (m, 1H, CH arom.)
33.2 (m)	5.4	−0.2	1.7	35.2 (m)	56.8 (d) *9*	1.18 (t, 3H, CH_3); 3.66 (q, 2H, CH_2); 3.93 (s, 1H, OH); 4.72 (s, 2H, CH_2); 7.73 (m, 1H, CH arom.)
27.5 (m) *20;9*		3.5 (t) *20*		33.5 (m) *20;9*	59.2 (d) *9*	1.59 (s, 6H, 2 CH_3); 3.91 (s, 3H, CH_3); 5.48 (s, 1H, OH); 8.00 (t, 1H, CH arom.)

TABLE 5

Experimental and spectral data for arylacetic amides **XII–XV**

	Yield (%)	M.p. or b.p. (°C/mmHg)	Molecular weight Found (Calcd.)	Empirical formula
$R_1 = H$, $R_2 = Ph$; $X = F^3$; $Y = NH_2$ (**XIIa**)	97	113–115 (benzene)[a]	317.0221 (317.0230)	$C_{14}H_8ClF_4NO$
$R_1 = H$, $R_2 = Ph$; $X = F^3$; $Y = NEt_2$ (**XIVa**)	70	132–134 (benzene)	373.0852 (373.0856)	$C_{18}H_{16}ClF_4NO$
$R_1 = H$, $R_2 = Ph$; $X = C_6F_5O$; $Y = NH_2$ (**XIIIa**)	94	91–92 (benzene)	481.0108 (481.0115)	$C_{20}H_8ClF_8NO_2$
$R_1 = R_2 = Ph$; $X = F^3$; $Y = NH_2$ (**XIIb**)	98	142–143 (CCl_4)	393.0537 (393.0543)	$C_{20}H_{12}ClF_4NO$
$R_1 = R_2 = Ph$; $X = F^3$; $Y = NEt_2$ (**XIVb**)	92	168–169 (benzene)	449.1153 (449.1169)	$C_{24}H_{20}ClF_4NO$
$R_1 = R_2 = Ph$; $X = C_6F_5O$; $Y = NEt_2$ (**XVb**)	95	160–162 (benzene)	613.1064 (613.1054)	$C_{30}H_{20}ClF_8NO_2$
$R_1 = H$, $R_2 = Bu^n$; $X = F^3$; $Y = NEt_2$ (**XIVc**)	90	71/0.25	353.1183 (353.1169)	$C_{16}H_{20}ClF_4NO$
$R_1 = R_2 = Et$; $X = F^3$; $Y = NH_2$ (**XIId**)	85	53–54 (CH_2Cl_2)	297.0537 (297.0544)	$C_{12}H_{12}ClF_4NO$
$R_1 = R_2 = Et$; $X = F^3$; $Y = NEt_2$ (**XIVd**)	55	viscous liquid	353.1183 (353.1169)	$C_{16}H_{20}ClF_4NO$
$R_1 = H$, $R_2 = CH_2OH$; $X = F^3$; $Y = NEt_2$ (**XIVe**)	83	viscous liquid	327.0633 (327.0649)	$C_{13}H_{14}ClF_4NO_2$
$R_1 = H$, $R_2 = CMe_2OH$ $X = F^3$; $Y = NH_2$ (**XIIf**)	77	136–137 (benzene)	299.0331 (299.0336)	$C_{11}H_{10}ClF_4NO_2$
$R_1 = H$, $R_2 = CMe_2OH$; $X = F^3$; $Y = NEt_2$ (**XIVf**)	67	glassy substance	355.0965 (355.0962)	$C_{15}H_{18}ClF_4NO_2$

[a]Recrystallization solvent.

^{19}F NMR spectra; chemical shifts (ppm) and J values (Hz)						^{1}H NMR spectra (ppm)
F^2	F^3 or			F^4	F^α	
	F^o	F^m	F^p			
28.6 (m)		4.1 (t) *20*		30.0 (m)	58.9 (d) *16*	7.41–7.57 (m, 5H, C_6H_5); 7.67 (m, 1H, CH arom.); 7.82 (s, 2H, NH_2)
27.8 (m)		3.7 (t) *20*		31.0 (m)	60.0 (d) *15*	1.14–1.30 (m, 6H, 2 CH_3); 2.98 (q, 2H, CH_2); 3.43 (m, 2H, CH_2); 7.34–7.52 (m, 5H, C_6H_5); 7.57 (m, 1H, CH arom.)
33.9 (m)	5.9	−0.4	1.2	36.1 (m)	57.6 (d) *16*	7.30–7.48 (m, 5H, C_6H_5); 7.53 (s, 2H, NH_2); 7.74 (t, 1H, CH arom.)
32.0 (d, d) *23;10*		2.1 (m) *23;21;2*		33.9 (m) *21*	59.8 (d, d) *10;2*	6.96–7.14 (m, 10H, 2 C_6H_5); 7.22 (d, 2H, NH_2)
31.4 (d, d) *23;10*		2.4 (m) *23;4*		35.7 (t, d) *23;10*	61.8 (d) *4*	1.27 (t, 6H, 2 CH_3); 3.07 (q, 4H, 2 CH_2); 7.00–7.15 (m, 10H, 2 C_6H_5)
38.5 (m)	6.0	0.0	1.6	41.7 (m)	61.4 (d) *4*	0.89 (t, 6H, 2 CH_3); 3.18 (q, 4H, 2 CH_2); 6.91–7.11 (m, 10H, 2 C_6H_5)
26.8 (m)		2.5 (t, d) *18;3*		27.7 (m)	60.1 (d) *14*	0.87 (t, 3H, CH_3); 1.14 (q, 6H, 2 CH_3); 1.31 (m, 2H, CH_2); 1.53 (m, 2H, CH_2); 2.60 (t, 2H, CH_2); 3.34 (t, 2H, CH_2); 3.70 (t, 2H, CH_2); 7.22 (m, 1H, CH arom.)
28.1 (d, d) *21;3*		−0.7 (m) *21;10*		31.5 (d, d) *21;10*	55.1 (s)	1.15 (t, 3H, CH_3); 1.19 (t, 3H, CH_3); 2.68 (m, 2H, CH_2); 2.83 (m, 2H, CH_2); 6.92 (d, 2H, NH_2)
28.1 (d, d) *22;9*		0.0 (m) *22*		29.4 (d, d) *22;9*	58.2 (s)	0.86 (t, 3H, CH_3); 1.01 (m, 9H, 3 CH_3); 2.54 (m, 2H, CH_2); 2.95 (m, 2H, CH_2); 3.07 (m, 2H, CH_2); 3.35 (m, 2H, CH_2)
27.7 (m)		2.6 (t) *18*		29.0 (m)	60.8 (d) *16*	1.20 (t, 6H, 2 CH_3); 2.87 (q, 4H, 2 CH_2); 4.53 (s, 1H, OH); 7.90 (m, 1H, CH arom.)
28.6 (m)		2.8 (t) *20*		32.4 (m)	59.8 (d) *14*	1.57 (s, 6H, 2 CH_3); 4.61 (s, 1H, OH); 6.94 (d, 2H, NH_2); 7.95 (t, 1H, CH arom.)
27.4 (m)		2.5 (t) *21*		28.7 (m)	62.1 (d) *12*	1.23 (t, 6H, 2 CH_3); 1.53 (s, 6H, 2 CH_3); 2.91 (q, 4H, 2 CH_2); OH not observed; 7.92 (m, 1H, CH arom.)

Preparation of N,N-*diethylamides* ***XIVa–f*** *and* ***XVb****: general procedure*

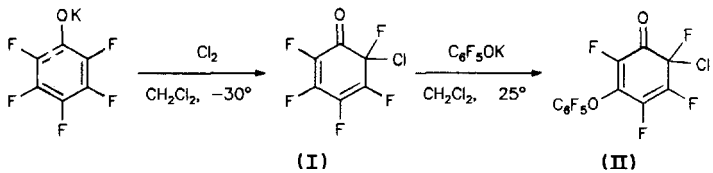
A two-fold molar excess of diethylamine was added dropwise at room temperature to a stirred solution of the cycloadduct (1–2 mmol) in benzene (20–40 ml) over 10–15 min, the reaction mixture was stirred for a further 45 min and evaporated. The residue was crystallized or distilled *in vacuo*.

Table 5 presents the experimental and spectral data for the arylacetic amides **XII–XV** obtained.

Results and discussion

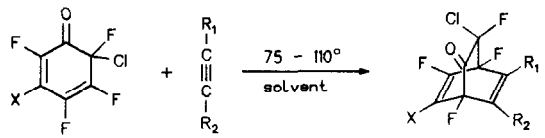
Polyfluorinated cyclohexa-2,4-dienones containing a halogen atom at a saturated carbon atom may be obtained by the halogenation of polyfluorinated phenols or their salts [3]. The ease of the reaction of polyfluorinated cyclohexadienones with nucleophilic agents, which leads to fluorine substitution at the double bond in the 3-position, allows further modification of compounds of this type by introducing various O- and N-substituents [1]. Thus, the reaction of potassium pentafluorophenoxide with chlorine (Scheme 1) gives dienone **I** [3], and further addition of equimolar amounts of potassium pentafluorophenoxide leads to dienone **II** [4].

We have found that polyfluorinated cyclohexadienones **I** and **II** undergo the Diels–Alder reaction of cyclodiene synthesis with acetylenes **IIIa–f** containing aryl and alkyl substituents (including an alcohol group), giving the stable cycloadducts **IVa–f** and **Va–f** in high yield (Scheme 2). The reactions proceed under relatively mild conditions at the boiling point of



(I) (II)

Scheme 1.



(I): X = F (IIIa): R_1 = H, R_2 = Ph (IVa–f): X = F
(II): X = C_6F_5O (IIIb): R_1 = R_2 = Ph (Va–f): X = C_6F_5O
(IIIc): R_1 = H, R_2 = Bu^n
(IIId): R_1 = R_2 = Et
(IIIe): R_1 = H, R_2 = CH_2OH
(IIIf): R_1 = H, R_2 = CMe_2OH

Scheme 2.

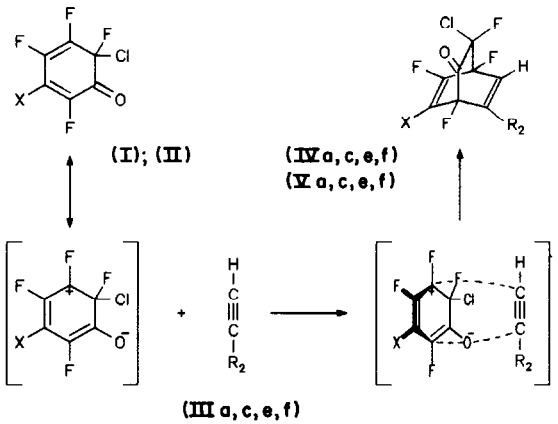
the solvent (carbon tetrachloride, benzene or toluene). The reaction time varies from 4 h to 30 h (Table 1).

The general structure of the bicyclo[2.2.2]octadienones **IVa–f** and **Va–f** was assigned to the Diels–Alder adducts on the basis of their ^{19}F NMR spectra which contain three groups of signals (Table 2). The low-field signals at 44–49 ppm have been assigned to fluorine atoms geminal to chlorine. The fluorine atoms at the double bond have a chemical shift of 7–17 ppm from hexafluorobenzene as a standard. The fluorine atoms at the bridgehead show very characteristic upfield chemical shifts (−33 to −46 ppm). All chemical shift values agree with the ^{19}F NMR spectral data for fluorines of the same type known from the literature [5].

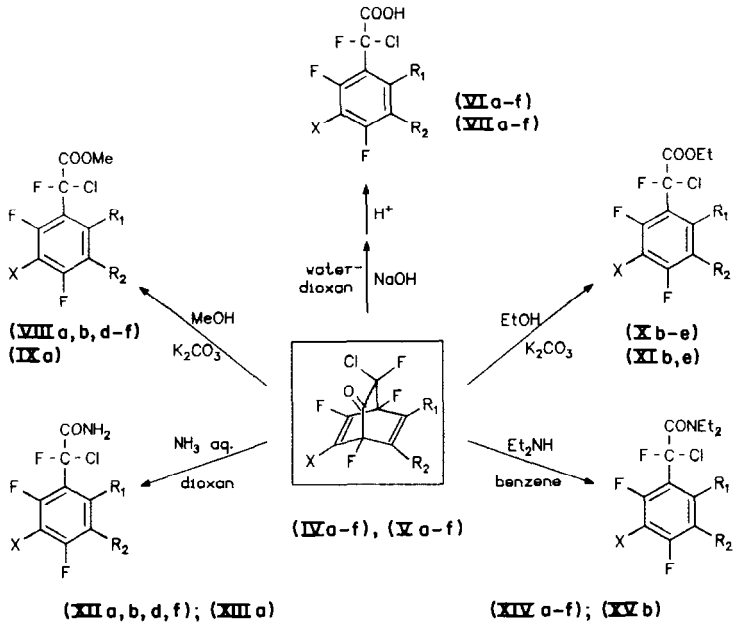
The spin–spin coupling constants of the cycloadducts and the structure of their aromatization products suggest that in all reactions with non-symmetric acetylenes **IIIa,c,e,f**, isomers with hydrogen in the 2-position are formed. Such orientation agrees with the electron density distribution in the diene and the dienophile (Scheme 3). Thus, the polyfluorinated cyclohexa-2,4-dienone molecule **I, II** is bipolar, with a positive charge localized on the carbon-5 atom. For this reason, compounds **I** and **II** react with dienophiles as electrophiles, attacking the unsubstituted carbon atom in acetylene derivatives according to Markovnikov's rule. The reactions are highly selective, with only one isomeric cycloadduct being formed initially.

However, during the isolation and purification of the initially formed cycloadducts, other isomers appear, possibly due to retrodiene synthesis. The formation of the same aromatic product from both isomers on reaction with nucleophilic reagents allows us to conclude that the other isomers under consideration are stereoisomers rather than structural ones. At present we are unable to identify the spatial structures of these isomers precisely and this problem is still under investigation.

An important property of the Diels–Alder adducts **IV** and **V** is their facile cleavage by nucleophilic reagents to form aromatic products (Scheme 4).



Scheme 3.

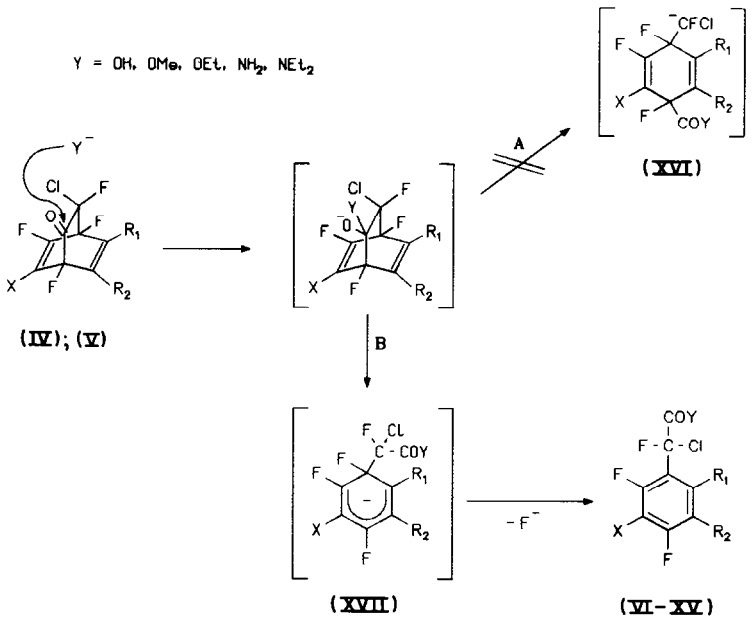


Scheme 4.

Thus, their treatment with an alkali in aqueous dioxan with subsequent acidification leads to the arylacetic acids **VI** and **VII**. Reaction with methanol or ethanol in the presence of potassium carbonate gives the aryl acetates **VIII**, **IX**, **X**, and **XI**. Reaction with aqueous ammonia in dioxan or with diethylamine in benzene leads to the amides **XII**, **XIII**, **XIV** and **XV**. All these reactions occur at room temperature.

The ^{19}F NMR data (Tables 3–5) confirm the structures of the arylacetic acid derivatives obtained in these reactions. The similarity of their chemical shifts indicates the presence of common structural fragments: the resonance of the tertiary (benzylic) fluorines at low field (55–63 ppm from hexafluorobenzene) agrees with published data [6] for similar fluorines; the chemical shifts of the aromatic fluorines correlate with the shifts in polysubstituted fluoroaromatic compounds [7].

The mechanism of aromatization of the bicyclic dienones **IV** and **V** may be represented as in Scheme 5. The nucleophilic species Y^- (or YH) initially attacks the carbonyl carbon atom of the Diels–Alder adducts. The intermediate formed as a result of this attack may be converted via route A or route B. Evidently, carbanion **XVI** with the negative charge localized on the carbon atom bonded to fluorine and chlorine will be destabilized in comparison to the cyclohexadienyl anion **XVII** with the delocalized negative charge. The structure of the reaction products **VI–XV** also indicates that route B is realized which includes the cleavage of the C(4)–C(8) bond to form a more stable anion **XVII** which undergoes fluoride ion elimination from the geminal group to give an aromatic compound.



Scheme 5.

The aromatization mechanism suggested has much in common with the well-known mechanism for haloform decomposition. A specific feature of this reaction is the preservation of the bridge structural elements in the final aromatic compound as opposed to the situation with the similar adducts formed in the analogous reactions of polyfluorinated cyclohexadienes [5] and non-fluorinated cyclohexadienones [8] with acetylene derivatives. The bicyclic adducts formed in the latter reactions lose their bridge on hydrolysis or thermolysis.

Conclusion

Many types of fluorine-containing arylacetic acid derivatives are potentially available by varying the substituents in the acetylene, in the geminal and 3-position of the polyfluorinated cyclohexadienones and by using various alcohols and amines at the aromatization stage of the Diels–Alder adducts. This method for the synthesis of fluorine-containing arylacetic acids developed by us and using polyfluorinated cyclohexadienones as substrates is an example of a general approach to the strategy of polyfunctional aromatic compound synthesis by transforming an available aromatic compound into a highly reactive non-aromatic system which, after modification, may be easily re-aromatized.

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