Formation of bicyclic adducts in the reactions of fluorinated 2,4-cyclohexadien-1-ones with 2-carboxybenzenediazonium

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Benzyne generated during the decomposition of 2-carboxybenzenediazonium interacts with 6-chloro-2,3,4,5,6-pentafluoro-2,4-cyclohexadien-1-one, 6-chloro-2,4,5,6-tetrafluoro-3-methoxy-2,4-cyclohexadien-1-one, 6-chloro-2,4,5,6-tetrafluoro-3-(pentafluorophenoxy)-2,4-cyclohexadien-1-one, and perfluoro-6-phenoxy-2,4-cyclohexadien-1-one to form [4+2]-cycloaddition products. The latter are easily converted to 1-naphthylacetic acid derivatives by the action of O- and N-nucleophiles.

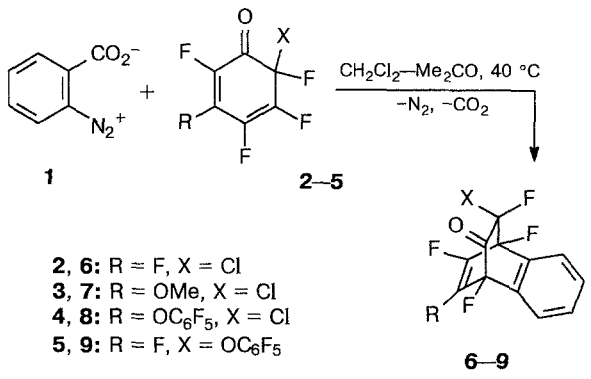
Key words: fluorinated 2,4-cyclohexadien-1-ones; 2-carboxybenzenediazonium; benzyne; [4+2]-cycloaddition; benzobicyclodienones; 1-naphthylacetic acid derivatives.

It has been shown previously[1] that polyfluorinated 2,4-cyclohexadien-1-ones undergo a Diels—Alder reaction with aryl- and alkylacetylenes to give [4+2]-cycloadducts in good yields. The latter can be readily converted into derivatives of phenylacetic acids. In the present work we studied the cycloaddition of polyfluorinated cyclohexadienones to benzyne and the aromatization of the cycloadducts to give fluoro derivatives of the naphthalene series.

As the precursor of benzyne, we employed 2-carboxybenzenediazonium (**1**), which is widely used[2] since it can be easily prepared *in situ* by diazotization of 2-aminobenzoic acid with alkyl nitrites[3] and has a relatively low decomposition temperature (~20 °C). This method of generating benzyne has been successfully used, for example, to carry out [4+2]-cycloaddition with hexamethyl-2,4-cyclohexadien-1-one.[4]

Decomposition of 2-carboxybenzenediazonium **1**, prepared *in situ*, in the presence of fluorinated cyclohexadienones **2—5** at 40 °C in a dichloromethane—acetone mixture (Scheme 1) affords products of [4+2]-cycloaddition of benzyne to compounds **2—5**, *i.e.*, cycloadducts **6—9**. The yields of benzobicyclooctadienones **6—9** isolated by column chromatography on silica gel amounted to 30, 37, 32, and 26 %, respectively, which is probably due to the high reactivity of fluorinated cyclohexadienones[5] and benzyne,[6] which give a variety of fluorine-containing by-products. Attempts to isolate and characterize these compounds were unsuccessful (according to TLC, the reaction mixtures contained no less than 6—7 products). The side products are readily resinified and remain on the chromatographic column.

Scheme 1



2, 6: R = F, X = Cl
3, 7: R = OMe, X = Cl
4, 8: R = OC_6F_5, X = Cl
5, 9: R = F, X = OC_6F_5

The structure of cycloadducts **6—9** was determined by comparing their ^{19}F NMR spectra with those of the adducts of substituted acetylenes with fluorinated 2,4-cyclohexadien-1-ones that we have described previously.[1] The ^{19}F NMR spectra of compounds **6—9** exhibit the characteristic high-field signals (−52 to −41 ppm with respect to C_6F_6) assigned to the bridgehead F atoms. The signals for the F atoms at the double bond are in the region 2—17 ppm, and those for the CFX groups are in the low field (43—52 ppm). In the IR spectra, absorption bands typical of vibrations of C=O and CF=CR bonds are observed (1720—1775 cm^{-1}).

Compounds **6—9** are formed as mixtures of two cycloadducts, which is indicated by the two sets of signals with similar chemical shifts corresponding to benzobicyclic adducts in the ^{19}F NMR spectra of the reaction mixtures. When a mixture of cycloadducts **6—9**

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 9, pp. 1634—1637, September, 1994.

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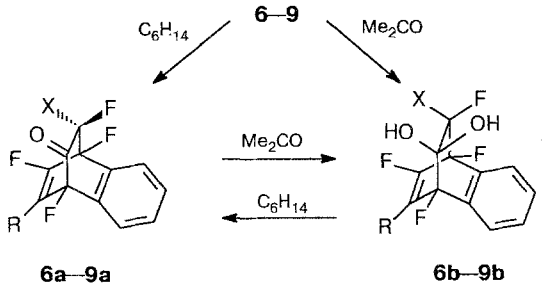
Scheme 2



isolated by chromatography is dissolved in hexane, adducts **6a—9a** are formed; in acetone they are converted into compounds **6b—9b** (within a period of several days to several weeks at room temperature). The individual products undergo similar transformations when the solvents are exchanged (Scheme 2).

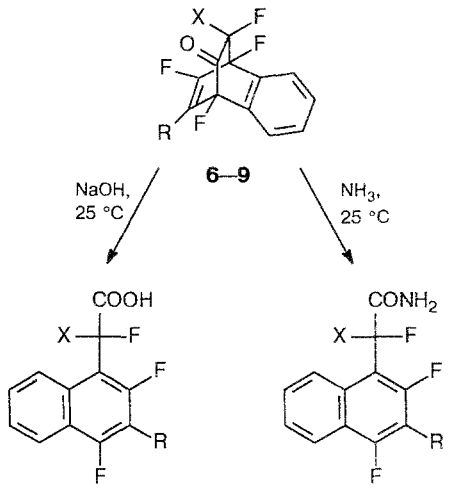
The spatial structure of adducts **6a—9a**, the F atom in which is directed towards the benzene ring (see Scheme 2), was determined from the preliminary data of X-ray diffraction analysis. Adducts **6b—9b** are presumably the hydrated forms of adducts **6a—9a**, which is indicated by the fact that their ^{13}C NMR spectra do not exhibit the signals typical of the C=O group (179—181 ppm) that are recorded in the spectra of compounds **6a—9a**, and exhibit signals for the $C(OH)_2$ group (107—108 ppm).

Fluorinated benzobicyclooctadienones **6—9**, similarly to fluorinated bicyclic dienones with alkyl or aryl substituents at the double bond,[1] readily undergo aromatization under the action of O- or N-nucleophiles but retain the structural units of the bridge that incorporates the carbonyl group. Treatment of compounds **6—9** with alkali or ammonia in aqueous dioxane at ~20 °C results in the formation of fluorine-containing 1-naphthylacetic acids (**10—13**) in high yields (90—96 %) or their amides (**14—17**) in yields of ~90 % (Scheme 3).

The structure of compounds **10—13** and **14—17** was confirmed by the similarity of their spectroscopic characteristics to the corresponding characteristics of fluorinated derivatives of phenylacetic acids.[1] For example, the ^{19}F NMR spectra exhibit low-field signals (58—62 ppm with respect to C_6F_6) for the F atom attached to the sp^3-hybridized carbon atom. The signals for the F atoms of the aromatic ring occur at a higher field (28—41 ppm), like the signals of the F atoms in other fluoroaromatic compounds.

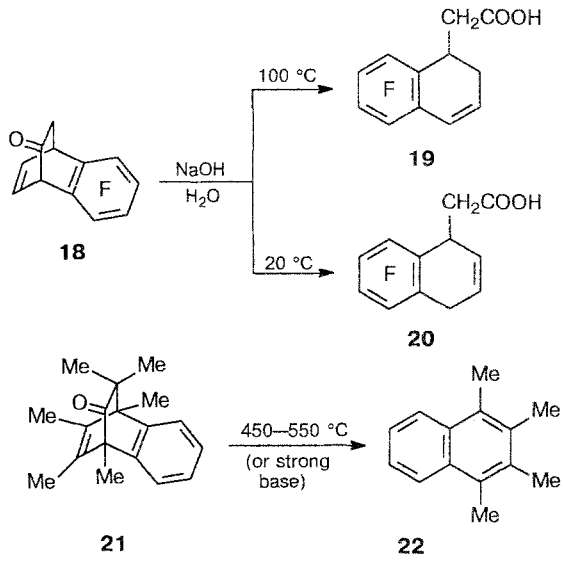
We have previously[1] considered the mechanism of aromatization of fluorine-containing bicyclic adducts, which involves elimination of the fluoride ion from the intermediate anionic σ-complex. It should be noted that the presence of a F atom at the bridgehead sp^3-hybridized carbon atom is likely to be a necessary condition for the aromatization of compounds **6—9**. For example, the reaction of benzobicyclodienone **18** (see Ref. 7) with aqueous NaOH both with boiling and at ~20 °C affords

Scheme 3

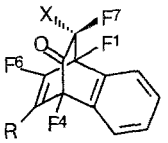
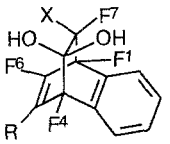


10, **14**: R = F, X = Cl
11, **15**: R = OMe, X= Cl
12, **16**: R = OC_6F_5, X = Cl
13, **17**: R = F, X = OC_6F_5

Scheme 4



1,2- and 1,4-dihydro derivatives **19** and **20**, rather than the naphthylacetic acids. At the same time, the adducts prepared by cycloaddition of dehydrobenzenes to hexamethyl-2,4-cyclohexadien-1-one (for instance, **21**) remain unchanged when treated with an aqueous solution of NaOH[4,8,9] and undergo aromatization to naphthalenes (**22**) through the action of strong bases (NaH, $NaCH_2SO_2Me$) or upon high-temperature (450—550 °C) thermolysis, as a result of elimination of the bridge incorporating the carbonyl group.[8]

Table 1. Spectral characteristics of cycloadducts **6a—9a**  and **6b—9b** 

Compound	^{19}F NMR, δ (*J*/Hz)								^{1}H NMR, δ	IR, ν/cm^{-1}	
	F-1	F-4	F-5	F-6	F-7	*o*-F	*m*-F	*p*-F		CR=CF	C=O
6a	−44.5 t (5)	−41.9 s	10.9 d (5)	6.8 s	49.3 d (5)				7.65—7.72 (m, CH arom.)	1745	1775
6b	−40.7 d (15)	−46.0 s	8.4 s	4.5 s	52.4 d (15)				7.43—7.51 (m, CH arom.)		
7a	−44.7 d (9)	−42.5 s		6.4 s	48.7 d (9)				4.05 (d, OCH_3); 7.36 (m, CH arom.)	1720	1770
7b	−41.3 d (12)	−46.8 s		3.9 s	51.0 d (12)				4.19 (d, OCH_3); 7.30 (m, CH arom.)		
8a	−45.2 d (10)	−42.8 s		17.5 s	46.4 d (10)	6.7	1.1	4.4	7.70—7.74 (m, CH arom.)	1730	1780
8b	−41.1 d (15)	−47.4 s		10.0 s	51.1 d (15)	7.8	−0.6	2.2	7.47—7.51 (m, CH arom.)		
9a	−52.2 d (10)	−49.7 s	9.1 s	4.6 s	45.2 m	7.9	0.5	6.5	7.46 (m, CH arom.)	1750	1775
9b	−51.0 d (3)	−51.1 s	8.2 s	2.0 s	43.4 m	9.6	−0.4	3.7	7.40 (m, CH arom.)		

Thus, it has been shown that fluorinated 2,4-cyclohexadien-1-ones **2—5** can react with benzyne as dienes to give Diels—Alder cycloadducts. When treated with nucleophiles the latter are converted into fluorinated derivatives of 1-naphthylacetic acid that retain the structural units of the bridge incorporating the carbonyl group.

Table 2. Characteristics of cycloadducts **6a—9a**

Cycloadduct	M.p./°C (from hexane)	*m/z*	Molecular formula	M_{calc}
6a	82—85	293.9865	$C_{12}H_4ClF_5O$	293.9871
7a	93—94	306.0063	$C_{13}H_7ClF_4O_2$	306.0070
8a	105—106	457.9757	$C_{18}H_4ClF_9O_2$	457.9756
9a	100—102	442.0054	$C_{18}H_4F_{10}O_2$	442.0051

Experimental

^{1}H and ^{19}F NMR spectra (200 and 188.28 MHz, respectively) were recorded on a Bruker WP-200 SY instrument in acetone-d_6 (with TMS and C_6F_6 as internal standards, respectively). IR spectra were measured on a Specord M-80 instrument (in KBr pellets for solids and in thin films for liquids). UV spectra were run on a Specord UV-VIS spectrophotometer

Table 3. Spectral and analytical data for acids **10—13** and amides **14—17**

Compound	^{19}F NMR, δ							^{1}H NMR, δ	M.p./°C (from C_6H_6)	*m/z* (M_{calc})	Molecular formula
	F-2	F-3	F-4	α-F	*o*-F	*m*-F	*p*-F				
10	35.8	5.0	28.3	58.7				7.62—7.68 (m, CH arom.); 10.82 (s, COOH)	145—146	291.9910 (291.9914)	$C_{12}H_5ClF_4O_2$
11	40.3		29.8	60.6				3.97 (s, OCH_3); 7.35 (m, CH arom.); 10.66 (s, COOH)	140—142	304.0122 (304.0114)	$C_{13}H_8ClF_3O_3$
12	41.2		30.6	60.4	6.0	0.2	1.9	7.70—7.76 (m, CH arom.); 11.18 (s, COOH)	133—134	455.9792 (455.9799)	$C_{18}H_5ClF_8O_3$
13	37.5	13.6	31.1	61.8	4.8	−0.4	2.4	7.27—7.34 (m, CH arom.); 10.90 (s, COOH)	128—129	440.0084 (440.0095)	$C_{18}H_5F_9O_3$
14	35.3	4.8	27.5	60.2				7.12 (s, NH_2); 7.60—7.68 (m, CH arom.)	149—152	291.0077 (291.0074)	$C_{12}H_6ClF_4NO$
15	40.0		29.6	61.3				4.00 (s, OCH_3); 6.95 (s, NH_2); 7.33—7.38 (m, CH arom.)	143—145	303.0280 (303.0274)	$C_{13}H_9ClF_3NO_2$
16	41.1		30.6	61.0	5.9	0.2	1.8	7.30 (s, NH_2); 7.69—7.75 (m, CH arom.)	118—120	454.9952 (454.9959)	$C_{18}H_6ClF_8NO_2$
17	37.2	13.4	29.8	62.2	5.0	−0.3	2.5	6.87 (d, NH_2); 7.25—7.31 (m, CH arom.)	122—123	439.0256 (439.0254)	$C_{18}H_6F_9NO_2$

for 10^{-1} *M* solutions in heptane. Molecular weights were determined on a MS-902 mass spectrometer (70 eV). The course of the reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates.

Fluorinated 2,4-cyclohexadien-1-ones **2**,[10] **4**,[11] and **5**[12] were prepared by the procedures described in the corresponding papers.

6-Chloro-2,4,5,6-tetrafluoro-3-methoxy-2,4-cyclohexadien-1-one (3). A solution of 6-chloro-2,3,4,5,6-pentafluoro-2,4-cyclohexadien-1-one (**2**) (5.45 g, 25 mmol) in 50 mL of CH_2Cl_2 was treated with an equimolar amount of MeOH (1 mL). The mixture was left overnight and concentrated. Vacuum distillation of the residue gave 4.90 g (85 %) of compound **3**, b.p. 65—66 °C (18 Torr). UV, λ_{max}/nm (ε): 236 (4680), 293 (1120), 316 (1150). IR, ν/cm^{-1}: 1610, 1655 (C=C); 1700 (C=O); 2870, 2970, 3025 (CH_3). ^{1}H NMR, δ: 4.35 (d, OCH_3). ^{19}F NMR, δ: −4.9 (m, F-2); 9.9 (dd, F-4); 13.1 (ddd, F-5); 38.2 (dt, F-6). MS, *m/z*: 229.9744 $[M]^+$. $C_7H_3ClF_4O_2$. Calculated: M = 229.9758.

Cycloadducts 6—9 (general procedure). A solution of 2-aminobenzoic acid (1.5 g, 10 mmol) in 10 mL of acetone was added dropwise to a boiling solution of cyclohexadienone **2—5** (10 mmol) and isoamyl nitrite (1.5 mL, 11 mmol) in 10 mL of CH_2Cl_2 over a period of 15 min. The mixture was boiled for an additional 15 min. After evaporation of the solvents, the residue was chromatographed on a column (1200×25 mm) with silica gel (100—160 μ) (using chloroform as the eluent) to afford cycloadducts **6—9** as yellowish oils (their spectroscopic data are presented in Table 1). Compounds **6—9** were dissolved in hexane and crystallized as isomers **6a—9a** by slow evaporation of the solvent (analytical data for these compounds are presented in Table 2).

Acids 10—13 (general procedure). At ~20 °C a solution of a 2.5-fold excess of NaOH in 3—5 mL of water was added dropwise to a stirred solution of a cycloadduct **6—9** (0.5—1.0 mmol) in 5—10 mL of dioxane over a period of 10—15 min. The mixture was stirred for an additional 15 min, poured into 15—25 mL of 5 % H_2SO_4, and extracted with ether. The extract was dried with $CaCl_2$ and concentrated. The residue was recrystallized from benzene.

Amides 14—17 (general procedure). At ~20 °C a 25 % solution of ammonia (0.5—1.0 mL) was added dropwise to a solution of a cycloadduct **6—9** (0.5—1.0 mmol) in 7.5—15 mL of dioxane. The mixture was stirred for 30 min, poured into 25 mL of water, and extracted with ether. The extract was dried with $CaCl_2$ and concentrated. The residue was recrystallized from CCl_4.

The analytical and spectroscopic data for acids **10—13** and amides **14—17** are listed in Table 3.

This work was carried out with the financial support of the International Science Foundation (Project No. Ch_2-6713-0925).

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Received April 14, 1994