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THE SYNTHESIS OF ANTIINFLAMMATORY α-(TRIFLUOROMETHYL)ARYLACETIC ACIDS

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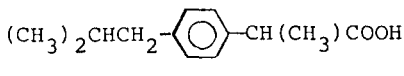
SUMMARY

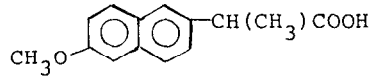
Several novel α-trifluoromethylarylacetic acids were synthesized, utilizing chloropentafluoroacetone as the source of the trifluoromethyl group. One of these new acids, the trifluoro-analog (30) of ibuprofen, showed antiinflammatory, analgesic, and ulcerogenic properties similar to ibuprofen.

INTRODUCTION

Many α-methylarylacetic acids, including ibuprofen and naproxen, are known to possess useful antiinflammatory and analgesic properties [1]. Although a large number of analogs of these compounds have been prepared, the corresponding α-(trifluoromethyl)arylacetic acids have not been reported. Such fluorine-containing derivatives would be expected to be more resistant to metabolic degradation, but their pharmacological properties are difficult to predict because of their greater acidity and altered solubility and transport characteristics. We have prepared several α-(trifluoromethyl)arylacetic acids, including the trifluoro-analog of ibuprofen and naproxen, and determined their antiinflammatory, analgesic, and ulcerogenic properties.



ibuprofen



naproxen

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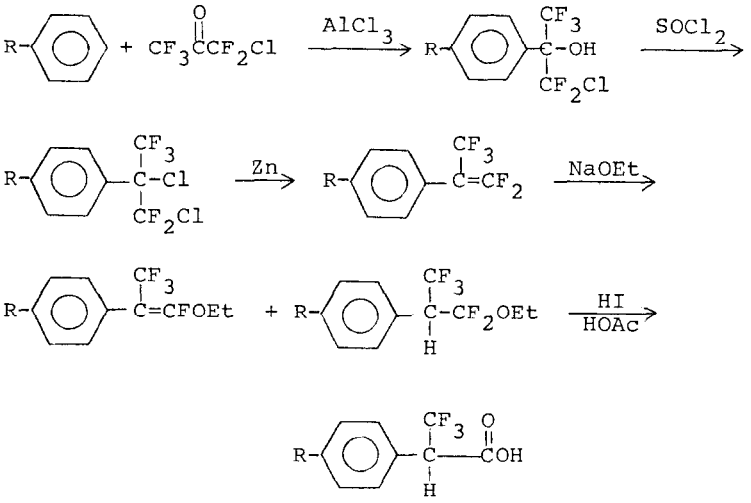
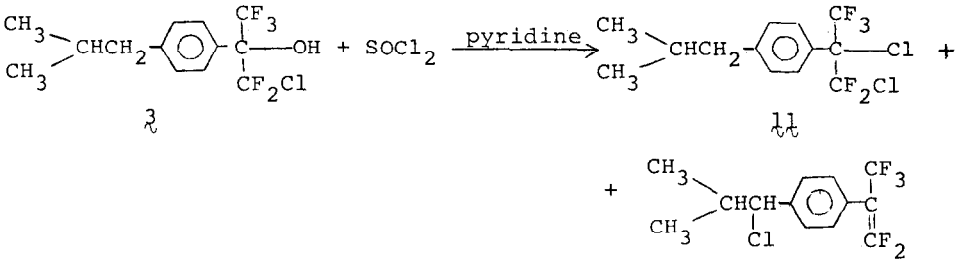
RESULTS AND DISCUSSION

Several α-trifluoromethylarylacetic acids were synthesized by the general method outlined in Scheme I.



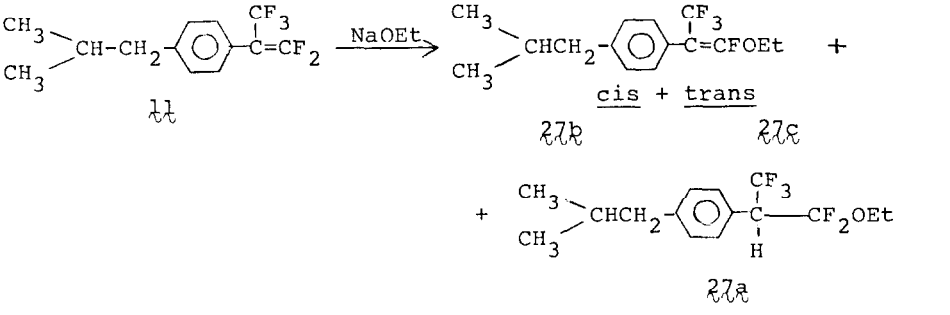
Scheme I

The 2-arylperfluoropropene (Table II) precursors to the α-CF_3 arylacetic acids were prepared in three steps as illustrated. The initial step was the Friedel-Crafts reaction of a substituted benzene with chloropentafluoroacetone in the presence of $AlCl_3$ to give 2-aryl-1-chloro-1,1,3,3,3-pentafluoro-2-propanols (Table I). Chlorination of this alcohol with thionyl chloride in the presence of pyridine (Table III) gave predominantly the 2-aryl-1,2-dichloro-1,1,3,3,3-pentafluoropropanes, but in some cases (for example 11 and 11a) chlorination at the benzylic position of the R substituent as well as loss of Cl_2 to give 2-arylpentafluoropropenes was also observed (Scheme II). It should be noted, however, that the components were separated for the purpose of identification only. The product mixtures may be converted directly to the desired fluoroolefins by dechlorination with zinc (Table II).



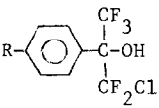
Scheme II

The α-trifluoromethylarylacetic acids (Table IV) were prepared from the 2-arylperfluoropropenes by reaction with an equivalent amount of sodium ethoxide in ethanol and subsequent hydrolysis (HI/HOAc) to the acids. The nucleophilic attack by EtO^- on the fluoroolefin occurs, as expected, exclusively on the $=CF_2$ group to give the CF_3-stabilized carbanion. The fate of the intermediate carbanion determines the nature of the products formed: proton abstraction from the solvent results in 2-aryl-1-ethoxy-1,1,3,3,3-pentafluoropropenes (27a for example); elimination of fluoride leads to cis and trans 2-aryl-1-ethoxy-1,3,3,3-tetrafluoropropanes. Pure samples of each component were separated by careful fractionation (See 27a,b,c), but the product mixture is suitable for conversion to the α-trifluoromethylarylacetic acids.



Scheme III

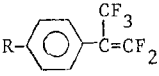
TABLE I

Aromatic alcohols Derived from CF_3COCF_2Cl (nc) R- 

No.	R	Procedure	Bp(mm)°C	Yield %	Formula	Anal.
1	$(CH_3)_3CCH_2$	A	85-86°(0.6)	60%	$C_{14}H_{19}ClF_5O$	C,H,F
2	$CH_3CH_2CH_2$	A	68(0.3)	44%	$C_{12}H_{11}F_5Cl$	C,H,F
3	$(CH_3)_2CHCH_2$	A	82-84(0.5)	82%	$C_{13}H_{14}ClF_5O$	C,H,Cl,F
4	cyclohexyl	A	100-103(0.2)	78%	$C_{15}H_{16}ClF_5O$	C,H,Cl,F
5	$(CH_3)_3C$	A	67-68(0.7)	60%	$C_{13}H_{14}ClF_5O$	C,H,Cl,F
6	$(CH_3)_2CH$	A	97-99(6)	62%	$C_{12}H_{12}ClF_5O$	C,H,Cl,F
7	a	B	b	38%	$C_{14}H_{10}ClF_5O_2$	C,H,Cl,F
8	H	c	76-77(11.2)	77%	$C_9H_6ClF_5O$	C,H,Cl,F

a. C_4H_6R=6-methoxynaphthyl. b. Mp=92-94°, recrystd. from hexane.
c. Prepared by Procedure A of Ref. [2].

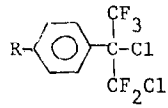
TABLE II

2-Aryl-1,1,3,3,3-pentafluoropropenes (nc) R- 

No.	R	Procedure	Bp(mm)°C	Yield %	Formula	Anal.
17	$(CH_3)_3CCH_2$	E	36°(15)	42	$C_{14}H_{15}F_5$	
18	$CH_3CH_2CH_2$	E	75°(8)		$C_{12}H_{11}F_5$	
19	$(CH_3)_2CHCH_2$	E	52-53°(1.2)	71	$C_{13}H_{13}F_5$	C,H,F
20	cyclohexyl	E[a]	66-68°(0.1)	60	$C_{15}H_{15}F_5$	C,H,F
21	$(CH_3)_3C$	E	71°(5.4)	64	$C_{13}H_{15}F_5$	C,H,F
22	$(CH_3)_2CH$	E	73-74°(10)	69	$C_{12}H_{11}F_5$	C,H,F
23	b	F	c	88	$C_{14}H_9F_5O$	C,H,F
24	H	E[d]	131-132°(20)	75	$C_9H_5F_5$	

a. Refluxed 18 hrs. b. C_4H_6R=6-methoxy naphthyl, c. mp 50-52°.
d. A side product, 1,3,3,3-tetrafluoro-1-methoxy-2-phenylpropene (24a), was isolated in 7% yield, bp 95-99° (20 mm).

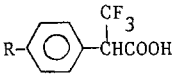
TABLE III

2-Aryl-1,2-dichloro-1,1,3,3,3-pentafluoropropanes (nc) 

No.	R	Procedure	Bp(mm)°C	Yield %	Formula	Anal.
9	$(CH_3)_3CCH_2$	C[b]	90(0.5)[a]	64%	$C_{14}H_{15}Cl_2F_5$	C,H
10	$CH_3CH_2CH_2$	C[c]	73(0.5)[d]	-	Mixture	-
11	$(CH_3)_2CHCH_2$	C[d]	72°(0.5)		$C_{13}H_{12}Cl_2F_5$	C,H,Cl,F
12	$(CH_3)_3C$	C[e]	86.8(1.6)	70%	$C_{13}H_{12}Cl_2F_5$	C,H,Cl,F
13	cyclohexyl	C[f]	120.121(1.5)	65%	$C_{15}H_{15}Cl_2F_5$	C,H,Cl,F
14	$(CH_3)_2CH$	C[g]	101-102(5.4)	60%	$C_{12}H_{11}Cl_2F_5$	C,H,Cl,F
15	h	D	i	57%		
16	H	j	69-70(7-8)	79%	$C_9H_5Cl_2F_5$	C,H,Cl,F

a. On cooling, the product solidified, mp 40-41°. b. A minor product in the crude mixture was 2-[4-(1-chloro-2,2-dimethylpropyl)phenyl)]1,1,3,3,3-pentafluoropropene. c. Spinning band distillation of a 60:40 crude mix. of the 1,2-dichloropentafluoropropane and the corresponding fluoropropene derivative gave an enriched mixture (83:17). This mixture was used in the next synthetic step. d. As above two major products, 37 and 58% of a mixture. However, cleanly separated by spin. band dist., see example. e. Refluxed 20 hrs. f. Refluxed 18 hrs. g. Reflux 24 hrs. h. C_4H_6R= 6-methoxynaphthyl. i. mp 61-63°. J. Prepared as in reference [2].

TABLE IV

α-(Trifluoromethyl)arylacetic acids (nc) 

No.	R	m.p.	Yield	Formula	Anal.	$^{19}F(CFCl_3)$
28	$(CH_3)_3CCH_2$	99-101°	83%	$C_{14}H_{17}F_3O_2$	C,H,F	δ-68.4(d,J=8.5Hz)
29	$CH_3CH_2CH_2$	40-45°	79%	$C_{12}H_{13}F_3O_2$	C,H,F	δ-68.3(d,J=8.5Hz)
30	$(CH_3)_2CHCH_2$	83-84°	88%	$C_{13}H_{15}F_3O_2$	C,H,F[b]	δ-67.3(d,J=8.5Hz)
31	$(CH_3)_3C$	93-96°	71%	$C_{13}H_{15}F_3O_2$	C,H,F	δ-68.2(d,J=8.5Hz)
32	cyclohexyl	144-145°	59%	$C_{15}H_{17}F_3O_2$	C,H,F	δ-68.2(d,J=8.5Hz)
33	$(CH_3)_2CH$	52-54°	71%	$C_{12}H_{13}F_3O_2$	C[c],H,F	δ-68.3(d,J=8.5Hz)
34	a	140-141°	4%	$C_{14}H_{11}F_3O_3$	C,H,F	δ-67.9(d,J=8.5Hz)
35[c]	H	73-75°	56%	$C_9H_7F_3O$	C,H,F	δ-68.1(d,J=8.5Hz)

a. 6-methoxy naphthyl. b. F, calcd., 21.90; found, 22.33. c. Previously prepared by a Wittig reaction [3].

PHARMACOLOGY

The α-trifluoromethylarylacetic acids of Table IV were tested for their antiinflammatory ability against established adjuvant-induced arthritis in male rats. Some of the compounds were also examined for analgesic and ulcerogenic properties in rodents. One of these acids, the trifluoro-analog (30) of ibuprofen, showed antiinflammatory, analgesic, and ulcerogenic properties similar to ibuprofen [4].

EXPERIMENTAL SECTION

The following synthetic procedures are representative for the preparation of compounds in Table I-IV. Where analyses are indicated only by symbols of the elements, results do not deviate more than ±0.4%. Fluorine NMR spectra were obtained on a Varian XL-100 instrument operated at 94.1 MHz using $CFCl_3$ as an internal standard. Upfield shifts are reported as negative values.

Procedure A. 1-Chloro-1,1,3,3,3-pentafluoro-2-[4-(2,2-dimethylpropyl)phenyl]-2-propanol (1)

A Hastelloy-lined steel shaker tube was charged with 50 g (0.34 mol) of neopentylbenzene and 3 g of aluminum chloride. The tube was cooled and evacuated and 46 g (0.25 mol) of chloropentafluoroacetone was added. The bomb was heated for 8 hr at 120°C, then cooled and vented to remove volatile materials. The black liquid obtained was filtered and then purified by spinning band distillation to give 49.95 g (60% yield) of 1 as a colorless liquid: bp 85° (.6 mm); ^{19}F NMR ($CDCl_3$) δ-62.2 ppm (q, J=11Hz, 2F), δ-73.9 (t, J=11Hz, 3F); ^{1}H NMR ($CDCl_3$) δ 7.38 ppm (A_2B_2, 4H), δ 3.34 (s, 1H), δ 2.50 (s, 2H), δ 0.90 (s, 9H).

Procedure B. 1-Chloro-1,1,3,3,3-pentafluoro-2-[2-(6-methoxy)-naphthyl]-2-propanol (7).

A mixture of 79.1 g (0.5 mol) of 2-methoxynaphthalene, 92 g (0.5 mol) of chloropentafluoroacetone, and 0.5 g of $AlCl_3$ was heated in a 360 ml Hastelloy-lined shaker tube at 120°C for 8 hr. The tube was cooled and vented and the solid contents were collected on a filter and washed with pentane. Sublimation of this solid at 120° (0.5 mm) gave 75 g of a sticky, white solid. Recrystallization from hexane gave 65.25 g (38% yield of 7 as colorless crystals: mp 92-94°; ^{19}F NMR ($CDCl_3$) δ-61.9 ppm (q, J=11Hz, 2F), δ-73.6 ppm (t, J=11Hz, 3F); ^{1}H NMR ($CDCl_3$) δ 3.70 ppm (s, 1H), δ 3.87 (s, 3H), δ 7.26 (m, 2H), δ 7.72 ppm (m, 3H) and 8.16 ppm (m, 1H).

Procedure C. Reaction of 1-chloro-1,1,3,3,3-pentafluoro-2-[4-(2-methylpropyl)-phenyl]-2-propanol with thionyl chloride

A mixture of 140 g (0.44 mol) of 1-chloro-1,1,3,3,3-pentafluoro-2-[4-(2-methylpropyl)phenyl]-2-propanol, 180 ml of thionyl chloride, and 5 ml of pyridine was refluxed for 44 hr. Most of the excess thionyl chloride was removed by distillation at atmospheric pressure. The solid that formed on cooling was filtered off, and the filtrate was distilled to give 130 g of a light yellow liquid, bp 65-73° (0.5 mm). GC analysis of the liquid showed two major products, 36.7% and 58.2%.

These two products were separated in pure form by careful fractionation. The material originally present as 36.7% in the mixture was isolated as a colorless liquid, bp 65-66° (0.5 mm) and identified as 1,1,3,3,3-pentafluoro-2-[4-(1-chloro 2-methylpropyl)phenyl]propene 11a: IR (1) 1739 cm^{-1}; ^{19}F NMR (CCl_3F) δ-76.4 ppm (q,d,J=24, 12.5Hz, 1F), δ-78.3 (q,d,J=11,2H Hz, 3F); ^{1}H NMR (CCl_3F) δ 0.84 ppm (d,J=6.5Hz, 3H), δ 1.05 (d, J=6.5Hz, 3H), δ 2.17 (m, 1H), δ 4.60 (d,J=7Hz, 1H) and δ 7.34 (A_2B_2). Anal. C, H, Cl, F.

The material originally present as 58.2% in the mixture was isolated as a colorless liquid, bp 72° (0.5 mm) and identified as 1-[1,2-dichloro-2,2-difluoro-1-(trifluoromethyl)-ethyl]-4-(2-methylpropyl)benzene 11: ^{19}F NMR (CCl_3F) δ -56.6 ppm ($\underline{ABX}_3$, J_{AB}=166Hz, J_{AX}=J_{BX}=12Hz) and δ-67.8 (t,J=12Hz 3F); ^{1}H NMR (CCl_3F) δ 0.87 ppm (d,J=7Hz, 2H) and δ7.46 (A_2B_2).

It is not necessary, however, to separate these two products for the purpose of this synthesis. As shown in Procedure E, the product mixture is a suitable starting material in the preparation of 19.

Procedure D. 1-[1,2-Dichloro-2,2-difluoro-1-(trifluoromethyl)-ethyl]-6-methoxynaphthalene (15)

A mixture of 58 g (0.17 mol) of 1-chloro-1,1,3,3,3-pentafluoro-2-[2-(6-methoxy)naphthyl]-2-propanol, (7) 100 ml of thionyl chloride, and 2 ml of pyridine was refluxed 4 hr and then cooled. Most of the thionyl chloride was removed by distillation at reduced pressure, and the syrupy residue was mixed with 300 ml of 50% aqueous sodium hydroxide. The insoluble suspended solid was collected on a filter, washed with water, dried, and then recrystallized from hexane to give 34.7 g (57%) of 15 as colorless crystals: mp 61-63°; ^{19}F NMR ($CDCl_3$) δ-56.2 ppm ($\underline{ABX}_3$) and -67.9 ppm ($AB\underline{X}_3$, J_{AB}=166Hz, J_{AX}= 12Hz, J_{BX}=11.5 Hz).

Procedure E. 1,1,3,3,3-Pentafluoro-2-[4-(2-methylpropyl)]-phenylpropene (19)

A solution of 130 g of a mixture of 11 and 11a in 100 ml of methanol was added dropwise to a suspension of 40 g of zinc dust and 1 g of zinc chloride in 300 ml of methanol. The reaction temperature was kept at 35-40° by controlling the rate of addition. The mixture was stirred overnight at room temperature and then filtered to remove the unreacted zinc. The filtrate was mixed with 1 ℓ of water and then extracted with CCl_3F. The extracts were dried over magnesium sulfate and distilled to give 55.12 g of 19 as a colorless liquid: bp 71-72° (4.6 mm).

This same product (19), prepared in 71% yield by using this procedure and starting with pure 11 was obtained as a colorless liquid: bp 52-53° (1.2 mm); ^{19}F NMR (CCl_3F) δ-59.9 ppm (d,d,J=11, 24Hz, 3F), δ-77.3 (d,q,J=14.5, 24Hz, 1F) and δ-79.2 (d,q,J=14.5, 11Hz, 1F).

Procedure F. 1,1,3,3,3-Pentafluoro-2-[(6-methoxy)naphthyl]-propene (23)

A solution of 30 g (0.083 mol) of 1-[1,2-dichloro-2,2-difluoro-1-(trifluoromethyl)ethyl]-6-methoxynaphthalene (15) in 300 ml of methanol was added dropwise to a stirred suspension of 10.5 g (0.16 mol) of zinc dust and 0.3 g of zinc chloride in 75 ml of methanol at 25°. The reaction mixture warmed spontaneously and was maintained below 40° by cooling. After the addition, the mixture was stirred for 1 hr and then filtered. The filtrate was mixed with 800 ml of dilute HCl,and the precipitate that formed was collected on a filter, washed with water and dried in air. Recrystallization from pentane (to separate from pentane-insoluble material) gave 21 g (88% yield) of 23 as colorless crystals: mp 50-52°; ^{19}F NMR ($CDCl_3$) δ-59.7 ppm (d,d,J=11, 24Hz, 3F), δ-76.4 (d,q,J=13,24Hz, 1F) and δ-78.4 (d,q,J=13, 11Hz, 1F).

Reaction of 1,1,3,3,3-pentafluoro-2-[4-(2-methylpropyl)phenyl]-propene with sodium ethoxide (27a,b,c) (nc)

A solution prepared by dissolving 4.6 g (0.2 g atom) of sodium in 250 ml ethanol was added dropwise to a stirred solution of 54 g (0.2 mole) of 1,1,3,3,3-pentafluoro-2-[4-(2-methylpropyl)phenyl]propene (11) in 200 ml ethanol cooled to 10°. The reaction mixture was then warmed to room temperature and mixed with 1 ℓ of water and 25 ml conc. hydrochloric acid. The organic layer was taken up in CCl_3F and dried ($MgSO_4$). GlC analysis showed three products in the ratio (A) 21:(B) 60:(C)19. Distillation gave a total of 47.9 g (79%) of product mixture, bp 74° (0.3 mm) separated by careful fractionation.

Component 27a was identified as ethyl 1,1,3,3,3-pentafluoro-2-[4-(2-methylpropyl)phenyl]propyl ether: bp 74-76° (0.3 mm); ^{19}F NMR (CCl_3F) δ-65.0 ppm (q,J=9.5 Hz, 3F) and -72.2 ppm (m, 2F). Anal. for $C_{15}H_{19}F_5O$, C, H, F.

Component 27b was identified as cis(CF_3,F)-1-ethoxy-1,3,3,3-tetrafluoro-2-[4-(2-methylpropyl)phenyl]propene: bp 79-80° (0.3 mm); ^{19}F NMR (CCl_3F) δ-57.4 ppm (d,J=24.5, 3F) and -72.2 ppm (m, 2F). Anal. for $C_{15}H_{19}F_5O$, C, H, F.

Component 27c was identified as trans(CF_3,F)-1-ethoxy-1,3,3,3-tetrafluoro-2-[4-(2-methylpropyl)phenyl]propene: bp 85-86° (0.4 mm); ^{19}F NMR (CCl_3F) δ-57.9 ppm (d,J=13.5Hz, 3F) and -78.8 ppm (q,J=13.5 ppm, 1F). Anal. for $C_{15}H_{18}F_4O$: C, H, F.

Procedure G. Preparation of 4-(2,2-dimethylpropyl)-α-(trifluoromethyl)benzeneacetic acid (28).

Part A. Reaction with sodium ethoxide

A solution of 10.55 g (0.04 mol) of 2-[4-(2,2-dimethylpropyl)phenyl]-1,1,3,3,3-pentafluoropropene (17) in 50 ml of ethanol was cooled to 10°C. A solution of sodium ethoxide, made by dissolving 0.92 g (0.04 g - atom) of sodium in 75 ml of ethanol, was added dropwise to the cooled solution. The reaction mixture was allowed to come to room temperature and mixed with 250 ml of water and 10 ml of conc. hydrochloric acid. The organic layer was taken up in Freon®-113, washed with water, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave 9.93 g of crude product. Analysis by G.C. shows the mixture to consist of three products in ratios 19:63:18. By analogy with related reaction (27a,b,c), one can designate the major product as the geometrical isomer in which the ethoxyl and CF_3 groups are trans to one another (the Z-isomer). However, separation of this mixture into its components was not necessary, and the crude product was used in the next step.

Part B. Hydrolysis

The mixture of products obtained in part A, 9.93 g, was hydrolyzed by refluxing in 11 g of 58% hydriodic acid and 40 ml of acetic acid for 24 hrs. The reaction mixture was cooled and mixed with water. The product precipitated as an oil which crystallized on cooling. Recrystallization from hexane gave 7.07 g of white crystals (mp 99-101°) identified as 28 ^{19}F NMR ($CFCl_3$), δ-68.4 ppm (d); ^{1}H NMR ($CFCl_3$), δ 0.92 ppm (s, 9H), δ2.50 ppm (s, 2H), δ 4.23 ppm (q, 1H, α-proton), δ 7.22 ppm (m, 4H), δ 12.08 ppm (s, 1H).

4-(n-Propyl)-α-(trifluoromethyl)benzeneacetic acid (29)

Part A. Reaction of 2-[4-(n-propyl)phenyl]-1,1,3,3,3-pentafluoropropene with sodium ethoxide

Experimental details are as in Part A of Procedure G, using 14.85 g (0.06 mol) of 2-[4-(n-propyl)phenyl]-1,1,3,3,3-pentafluoropropene (18) in 50 ml of ethanol and 1.36 g (0.06 g atom) of sodium in 75 ml of ethanol. The crude product mixture is used in Part B.

Part B. Hydrolysis

Experimental details are as in Part B of Procedure G, with 12.76 g of the mixture obtained in Part A, 11 g of 58% hydriodic acid and 40 ml of acetic acid. In the workup, addition of water resulted in the formation of an oily precipitate which did not crystallize on cooling. The viscous liquid was treated with 2% sodium bicarbonate solution, washed with ether, acidified with 10% HCl and extracted with Freon®-113. The organic extract was washed with water, dried,and evaporated to dryness at reduced pressure to give 2.23 g of 29: mp 40-45°; ^{19}F NMR ($CDCl_3$) δ-68.3 ppm (1). ^{1}H NMR ($CDCl_3$) δ7.30 ppm (m, 4H), δ4.30 (q, 1H), δ 2.62 (t, 2H), δ 1.3-1.9 (m, 2H), δ 0.95 (t, 3H); ir (KBr) 5.80μ (acid carbonyl), 7.5-9.0μ (s) C-F region.

4-(2-Methylpropyl)-α-(trifluoromethyl)benzeneacetic acid (30)

A mixture of 44 g (0.2 mol) of 58% hydriodic acid, 42 g (ca. 0.14 mol) of a mixture of 27a,b and c (recombined in the ratio of 27:49:22) and 150 ml acetic acid was refluxed for 24 hr and then cooled and poured into 1 ℓ of water. The solid that precipitated was collected on a filter, dried in air, and recrystallized from hexane to give 32.0 g (88%) of 30 as colorless crystals: mp 83-84°; ^{19}F NMR ($CDCl_3$) δ-67.3 ppm (d, J=8.5Hz); ^{1}H NMR ($CDCl_3$) δ 0.87 ppm (d, J=6Hz, 6H), 1.80 ppm (m, 1H), 2.40 ppm (d, J=6Hz, 2H), 4.18 ppm (q, J=8.5, 1H), 7.03 ppm (A_2B_2) and 11.5 ppm (s, 1H). Anal. ($C_{13}H_{15}F_3O_2$), C,H,F.

4-Cyclohexyl-α-(trifluoromethyl)benzeneacetic acid (32)

Part A. See Procedure G, Part A. Reactants were 23.22 g (.08 mol) of 1,1,3,3-pentafluoro-2-(4-cyclohexylphenyl)propene (20) in 100 ml of ethanol and 1.84 g (0.08 g-atom) of sodium in 110 ml of ethanol. A colorless liquid mixture of three products was obtained and used in Part B.

Part B. The liquid product from Part A was dissolved in 85 ml of acetic acid containing 26 g (0.12 mol) of 58% HI,and the solution was refluxed 18 hrs. The reaction mixture was cooled and then poured into 600 ml of ice water. The solid that precipitated was collected on a filter, washed with water,and then recrystallized from hexane to give 13.49 g (59%) of 32 as colorless crystals: mp 144-145°; ^{19}F NMR (CCl_3D) δ-68.2 ppm (d, J=8.5Hz); Anal. ($C_{15}H_{17}F_3O_2$), C,H,F.

4-(1,1-Dimethylethyl)-α-(trifluoromethyl)benzeneacetic acid (31)

A solution of 1.1 g (0.047 g-atom) of sodium in 70 ml ethanol was added dropwise to a stirred solution of 12.4 g (0.047 mole) of 1,1,3,3,3-pentafluoro-2-[4-(1,1-dimethylethyl)phenyl]propene (21) in 70 ml of ethanol. The reaction

mixture was stirred for 1 hr at room temperature, and then poured into 300 ml of water. The aqueous mixture was extracted with CCl_3F, and the extracts were dried ($MgSO_4$) and then evaporated to dryness under reduced pressure to give 11.23 g of a colorless mixture of 3 components. This residue was dissolved in 50 ml of acetic acid, and 15.3 g (0.07 mole) of 58% hydriodic acid was added. The resulting solution was refluxed for 20 hr, and then cooled and poured into 300 ml of ice water. The solid that precipitated was collected on a filter, washed with water, and recrystallized from pentane (cooled to -70°) to give 7.3 g (60%) of 31 as colorless crystals: mp 95-97°; ^{19}F NMR (CCl_3D) δ-68.2 ppm (d, J=8.5Hz); ^1H NMR (CCl_3D) δ 1.32 (s, 9H), 4.28 ppm (q, J=8.5Hz, 1H), 7.36 ppm (s, 4H) and 11.8 ppm (s, OH). A second crop of crystals, mp 93-96°, raised the total yield to 71%. Anal. ($C_{13}H_{15}F_3O_2$): H, F; C, calcd, 60.00; found 60.87.

4-(1-Methylethyl)-α-(trifluoromethyl)benzeneacetic acid (33)

A solution of 0.92 g (0.04 mole) of sodium in 65 ml ethanol was added dropwise to a stirred solution of 10.0 g (0.04 mole) of 1,1,3,3,3-pentafluoro-2-[4-(1-methylethyl)-phenyl]propene (22) in 65 ml of ethanol. The reaction mixture was stirred at room temperature (25°) for 1 hr, and then poured into 300 ml water. The aqueous mixture was extracted with CCl_3F. The extracts were dried ($MgSO_4$), and the CCl_3F was distilled off to give 9.3 g of colorless liquid (GLC analysis indicated three components in the ratio 22.5:61.5:5.16 This liquid was dissolved in 40 ml of acetic acid containing 13 g of 58% HI, and this solution was refluxed for 18 hr, and then cooled and poured into 300 ml ice water. The aqueous mixture was extracted with CCl_3F, and the extracts were washed with water and dried ($MgSO_4$). The CCl_3F was removed by evaporation under reduced pressure to give 7.0 g (71%) of 33 as a white crystalline residue: mp 52-54°; ^{19}F NMR (CCl_3D) δ-68.3 ppm (d, J=8.5Hz); ir (KBr) 5.83μ (C=O). Anal. ($C_{12}H_{13}F_3O_2$) H, F; Calcd. C 58.54; Found C, 59.41.

6-Methoxy-α-(trifluoromethyl)-2-naphthaleneacetic acid (34)

A solution prepared by dissolving 2.35 g (0.06 mole) of potassium in 60 ml t-butyl alcohol was added dropwise to a solution of 17.3 g (0.06 mole) of 1,1,3,3,3-pentafluoro-2-[2-(6-methoxy)naphthyl]propene (23) in 150 ml of t-butyl alcohol at 25°. The reaction mixture was stirred at 25° for 1 hr, and the solid precipitate that formed was filtered off. The filtrate was evaporated to dryness under reduced pressure to give a tarry residue. The residue was extracted with 100 ml of 5% aqueous $NaHCO_3$ solution, and the extracts were filtered and then acidified with 10% HCl. The precipitate that formed was collected on a filter, washed with water, and recrystallized from benzene-hexane to give 650 mg (4% yield) of 6-methoxy-α-(trifluoromethyl)-2-naphthaleneacetic acid (34) as colorless crystals: mp 140-141°; ^{19}F NMR ($CDCl_3$) δ-67.9 ppm (d, J=8.5Hz); ^1H NMR ($CDCl_3$) δ 3.93 ppm (s, 3H), 4.49 ppm (q, J=8.5Hz, 1H), 7.5 ppm (m, 6H) and 10.62 ppm (s, OH). Anal. ($C_{14}H_{11}F_3O_3$)C,H,F.

α-(Trifluoromethyl)benzeneacetic acid (35)

A solution of 5.9 g (0.15 g atom) of potassium in 120 ml t-butyl alcohol was added dropwise to a solution of 31.2 g (0.15 mole) of 1,1,3,3,3-pentafluoro-2-phenylpropene (24) in 50 ml of t-butyl alcohol at 20-30°. The reaction mixture was stirred at 25° for 2 hr, and then poured into 500 ml water. The aqueous mixture was extracted with 200 ml CCl_3F, and the extracts were dried ($MgSO_4$). The solvent was removed by slowly raising the temperature to 100° and holding it there for 4 hr. The white solid that formed on cooling was collected on a filter and recrystallized from hexane to give 7.7 g (19%) of 35 as colorless crystals: mp 73-75°; ir (KBr) 5.78μ (C=O).

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