tallization of the colorless product fraction from benzene gave 0.037 g (9%) of product, mp 142–143 °C dec.

Anal. Calcd for $C_{17}H_{12}N_4O_8$: C, 51.01; H, 3.02; N, 14.00. Found: C, 51.00; H, 2.93; N, 14.16.

9,10-Dimethyl-11,11,12,12-tetranitro-9,10-dihydro-9,10-ethanoanthracene (3). A solution of 0.30 g (1.0 mmol) of hexanitroethane and 0.41 g (2.0 mmol) of 9,10-dimethylanthracene in 10.0 mL of benzene was refluxed 30 min under nitrogen. The above isolation procedure gave 0.097 g (23%) of **3**, mp 142–143 °C dec.

Anal. Calcd for $C_{18}H_{14}N_4O_8$: C, 52.18; H, 3.41; N, 13.52. Found: C, 52.39; H, 3.44; N, 13.95.

5,5,6,6-Tetranitro-2-norbornene (4). To a solution of 2.0 mL of cyclopentadiene and 2.0 mL of methylene chloride cooled to −20 °C was added, dropwise over 20 min, 0.30 g (1.0 mmol) of hexanitroethane in 2.0 mL of methylene chloride. The resulting orange solution was stirred for 2 h at −10 °C and 0.5 h at 0 °C. Concentration in vacuo of the resulting solution gave a gummy, dark residue which was chromatographed on 30 g of silica gel (hexane–methylene chloride). The colorless early fractions were rechromatographed over 10 g of silica gel (hexane–methylene chloride). Recrystallization from hexane–benzene gave 0.042 g (15%) of colorless needles, mp 127–129 °C.

Anal. Calcd for $C_7H_6N_4O_8$: C, 30.67; H, 2.21; N, 20.44. Found: C, 31.12; H, 2.28; N, 20.43.

12-Nitro-9,10-dihydro-9,10-ethanoanthracen-11-one Sodium Salt (5). A solution of 0.625 g (4.0 mmol) of sodium iodide in 5 mL of 1,2-dimethoxyethane was added to 0.484 g (1.0 mmol) of the anthracene–tetranitroethylene adduct (benzene solvate) in 3 mL of 1,2-dimethoxyethane, and the mixture was heated with stirring at 60–65 °C for 4 h. The resulting precipitate was filtered, washed with 1,2-dimethoxyethane and with methylene chloride, and air dried to give 0.288 g (87%) of an off-white solid, mp 295 °C dec, the dimethoxyethane solvate of the title compound containing 0.5 mol of solvent: IR (KBr) 3450, 1650, 1405, 1280 cm^{-1}; NMR (Me_2SO-d_6) δ 7.10 (m, 8 H, aromatic), 5.70 (s, 1 H, CH), 4.68 (s, 1 H, CH), 3.38 (s, 2 H, CH_2 of solvent), 3.20 (s, 3 H, CH_3 of solvent).

12-Nitro-9,10-dihydro-9,10-ethanoanthracen-11-one (6). A suspension of 0.25 g (0.75 mmol) of the above sodium salt in 6 mL of methylene chloride was acidified dropwise with stirring at 5 °C with 0.048 g (0.80 mmol) of glacial acetic acid in 1 mL of methylene chloride. The mixture was stirred at 5 °C for 1 h and filtered. The filter cake was washed with methylene chloride, and the combined methylene chloride solutions were stripped of solvent under vacuum to give a solid residue which was triturated with benzene–hexane and filtered to give 0.096 g (48%) of white crystals, mp 170–174 °C dec. An analytical sample, mp 181–182.5 °C dec, was prepared by silica gel chromatography (methylene chloride) followed by recrystallization twice from benzene–hexane: IR (CH_2Cl_2) 1760, 1560, 1370 cm^{-1}; NMR ($CDCl_3$) δ 7.27 (m, 8 H), 4.95 (m, 3 H).

Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.51; H, 4.22; N, 5.25.

12-Chloro-12-nitro-9,10-dihydro-9,10-ethanoanthracen-11-one (7). A suspension of 0.225 g (0.68 mmol) of the nitronate salt solvate (**5**) in 15 mL of methylene chloride was chlorinated at 0 °C until the yellow chlorine color persisted in the solution. The chlorine flow was discontinued, and the mixture was stirred for 20 min at 0 °C and then filtered. The filtrate was concentrated in vacuo and the solid residue was recrystallized twice from benzene–hexane to give 0.080 g (39%) of colorless crystals: mp 161.5–162 °C; IR (CH_2Cl_2) 1760, 1570, 1460, 1340 cm^{-1}; NMR ($CDCl_3$) δ 7.27 (m, 8 H), 5.02 (s, 1 H), 4.97 (s, 1 H).

Anal. Calcd for $C_{16}H_{10}NClO_3$: C, 64.12; H, 3.36; N, 4.67; Cl, 11.83. Found: C, 64.10; H, 3.44; N, 4.56; Cl, 12.07.

12-Bromo-12-nitro-9,10-dihydro-9,10-ethanoanthracen-11-one (8). To a suspension of 0.20 g (0.60 mmol) of the nitronate sodium salt solvate (**5**) in 10 mL of methylene chloride was added, dropwise at 5 °C, 0.096 g (0.60 mmol) of bromine in 5 mL of methylene chloride with stirring over a 35-min period. The orange mixture was stirred for 30 min. The above isolation procedure gave 0.12 g (42%) of colorless crystals: mp 168–169.5 °C; IR (CH_2Cl_2) 1760, 1560, 1465, 1340 cm^{-1}; NMR ($CDCl_3$) δ 7.22 (m, 8 H), 5.15 (s, 1 H), 4.98 (s, 1 H).

Anal. Calcd for $C_{16}H_{10}BrNO_3$: C, 55.84; H, 2.93; N, 4.07; Br, 23.22. Found: C, 55.89; H, 3.22; N, 3.77; Br, 23.43.

Registry No. 1, 73804-83-8; 2, 73804-84-9; 3, 73804-85-0; 4, 73804-86-1; 5, 73804-87-2; 6, 73804-88-3; 7, 73804-89-4; 8, 73804-90-7; hexanitroethane, 918-37-6; anthracene, 120-12-7; 9-methylanthracene, 779-02-2; 9,10-dimethylanthracene, 781-43-1; cyclopentadiene, 542-92-7.

α,α-Difluoroarylacetic Acids: Preparation from (Diethylamino)sulfur Trifluoride and α-Oxoarylacetates

W. J. Middleton* and E. M. Bingham

Central Research & Development Department, Experimental Station, E. I. du Pont de Nemours & Co., Inc., Wilmington, Delaware 19898

Received April 23, 1980

Several α,α-difluoroarylacetic acids have been prepared by reaction of DAST ((diethylamino)sulfur trifluoride) with esters of α-oxoarylacetic acids and then hydrolysis of the resulting difluoro ester. Examples include the α,α-difluoro derivatives of the synthetic plant auxin, α-naphthylacetic acid, and the antiinflammatory drug, ibufenac.

We have found a convenient and high yield one-step method for preparing esters of α,α-difluoroacetic acids by the selective replacement of the α-oxo group of α-oxoarylacetates with two fluorine atoms, using the fluorinating reagent DAST[1] ((diethylamino)sulfur trifluoride). Such fluorine-containing compounds are virtually unknown, possibly because of the absence of a good general synthetic route. The only reported ester of an α,α-difluoroarylacetic acid is ethyl difluorobenzeneacetate; its six-step low-yield (13.3%) synthesis starts with the chlorination of phenylacetonitrile and involves halogen-exchange and hydrolysis steps.[2]

These rather inaccessible compounds are of interest because the presence of two fluorine atoms at the α position would be expected to modify the activity of biologically important arylacetic acids. Naturally occurring

(1) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574; U.S. Patent 3976691, 1976.

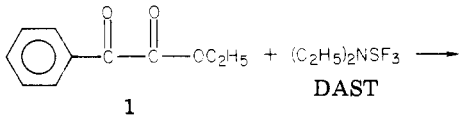
(2) Yagupol'skii, L. M.; Belinskaya, R. V. *Zh. Obshch. Khim.* **1958**, *28*, 772.

0022-3263/80/1945-2883$01.00/0

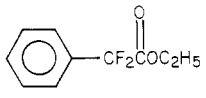
arylacetic acids and their derivatives include plant hormones and antibiotics. Synthetic examples include many pharmaceutical and agricultural chemicals.

Results and Discussion

Ethyl difluorobenzeneacetate (**2**) was prepared by stirring a mixture of ethyl phenylglyoxylate (**1**) and DAST without solvent at ambient temperature for several hours. Aqueous workup to remove the byproducts and then distillation gave **2** in 92% yield.



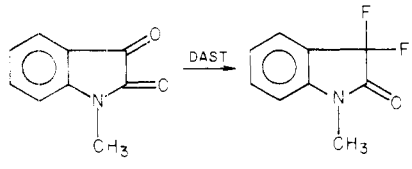
1



2

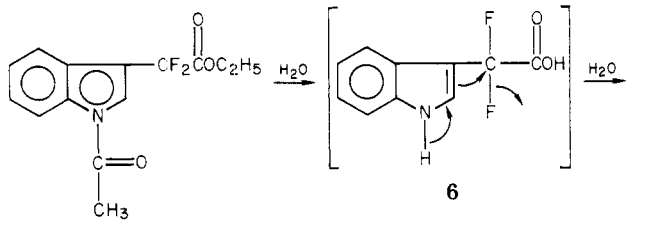
This reaction appears to be very general. Several esters of α-oxoarylacetic acids that have been converted to the corresponding esters of α,α-difluoroarylacetic acids are listed in Table I. In some cases, mild heating (up to 60 °C) was used to speed the reaction, but caution must be used since DAST can decompose violently at temperatures above 90 °C.[3]

The α-oxo group of α-oxoarylacetamides can also be selectively replaced with fluorine. This was demonstrated by the ready conversion of *N*-methylisatin (**3**) to the difluoro derivative **4** by reaction with DAST.

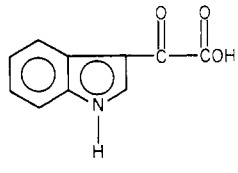


3 4

Most of the difluoro esters prepared in this study were converted to the free acid, by either acidic or basic hydrolysis. Table II contains a list of the acids prepared in this manner. As expected, the acids are all very acidic; the pK_a of α,α-difluorobenzeneacetic acid in 40% ethanol is 2.87 compared to a pK_a of 4.28 for benzeneacetic acid. The α-fluoro substituents of these acids were stable to hydrolysis under both acidic and basic conditions. However, attempts to prepare α,α-difluoroindoleacetic acid (**6**) by hydrolysis of the ester **5**, resulted also in the hydrolysis of the fluorine groups and the regeneration of a carbonyl group (**7**). The fluorine atoms in **6** are apparently very susceptible to hydrolysis because of activation by the indole nitrogen.

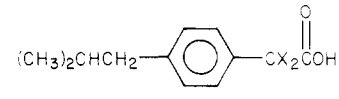


5 6

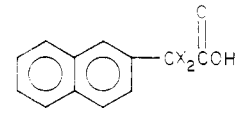


7

Two of the α,α-difluoroarylacetic acids prepared are analogues of known biologically active compounds. **8a** is the difluoro analogue of the synthetic antiinflammatory drug ibufenac (**8b**), and **9a** is the difluoro analogue of the synthetic plant-growth regulant α-naphthylacetic acid (**9b**).



8a, X = F
b, X = H



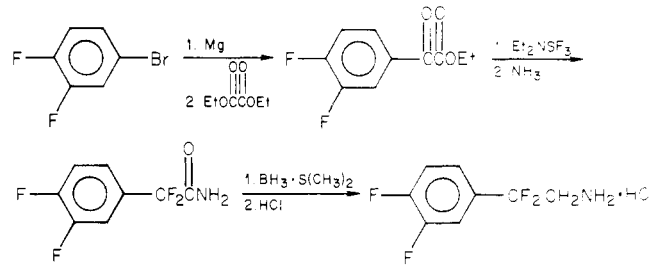
9a, X = F
b, X = H

Fluorine in these molecules appears to have an unpredictable effect. Biological testing has shown that **8a** is essentially inactive as an antiinflammatory agent; but **9a** is a plant-growth regulant comparable to **9b**.

The new α-oxoarylacetates used in this study were prepared by the reaction of the corresponding aryllithium or aryl Grignard and ethyl oxalate and are listed in Table IV.

Other derivatives were also prepared from the difluoro esters, including amides (Table III), acid chlorides, and nitriles. Phenethylamines were prepared by reduction of α,α-difluoroarylacetamide with borane methyl sulfide as illustrated in Scheme I.

Scheme I



Experimental Section

Proton NMR spectra were obtained on a Varian A-60 instrument with Me_4Si as an internal standard. Fluorine NMR spectra were obtained on a Varian XL-100 instrument operated at 94.1 MHz with $CFCl_3$ as an internal standard. Downfield shifts are reported as positive values.

Alkyl α,α-Difluoroarylacetates (Table I). Alkyl α,α-difluoroarylacetates listed in Table I were prepared by stirring mixtures of α-keto esters with DAST (**caution**)[3] at ambient temperatures or slightly elevated temperatures (40–60 °C) until all of the ester was converted (GLC). The reaction mixtures were worked up by pouring slowly into ice–water. Solid products were purified by recrystallization, and liquid products were extracted with CCl_3F and distilled. The following are typical examples.

Ethyl α,α-Difluoro-4-phenylbenzeneacetate. A mixture of 25.4 g (0.1 mol) of ethyl α-oxo-4-phenylbenzeneacetate and 25 mL (0.2 mol) of DAST was stirred together. The temperature rose slowly to 45 °C and then cooled. The reaction mixture was stirred for an additional 2 h at room temperature and then poured over ice. The oil that formed was taken up in CCl_3F, washed with water, dried ($MgSO_4$), and distilled to give 23.5 g (92%) of ethyl α,α-difluoro-4-phenylbenzeneacetate as a colorless liquid that solidified on cooling to a colorless solid: mp 27 °C; IR (KBr) 5.63 μm (C=O).

Ethyl 1-(4-Chlorobenzoyl)-α,α-difluoro-3-indoleacetate. A mixture of 23.1 g (0.065 mol) of ethyl 1-(4-chlorobenzoyl)-α-oxo-3-indoleacetate and 12.6 mL (0.1 mol) of DAST was heated at 80–90 °C for 3 h and then cooled. The solidified reaction

(3) PCR, Inc., has withdrawn DAST from sale because of explosions they have experienced in its production. See: Cochran, J.; *Chem. Eng. News* **1979**, March 19, p 4. However, we believe DAST is safe to use provided suitable precautions are taken. See: Middleton, W. J. *Ibid.* May 21, p 43.

Table I. Alkyl α,α-Difluoroarylacetates ($ArCF_2CO_2R$)

Ar	R	formula	yield, %	bp, °C (mm)	^{19}F NMR, δ (solvent)	anal.[a]
phenyl	Et	$C_{10}H_{10}F_2O_2$	92	75-78 (3)	−103.9 ($CFCl_3$)	C, H, F
phenyl	CH_3	$C_9H_8F_2O_2$	73	100-101 (20)	−104.38 ($CFCl_3$)	C, H
3,4-difluorophenyl	Et	$C_{10}H_8F_4O_2$	65	100-101 (20)	−103.99, −134.03, −135.96 ($CFCl_3$)	C, H
4-(trifluoromethyl)phenyl	Et	$C_{11}H_9F_5O_2$	74	83-84 (5)	−105.0, −63.9 ($CFCl_3$)	C, H, F
4-(perfluoroisopropyl)phenyl	Et	$C_{13}H_9F_9O_2$	75	77-78 (1.6)	−104.8, −76.1, −182.9 ($CFCl_3$)	C, H, F
4-biphenylyl	Et	$C_{16}H_{14}F_2O_2$	92	152-154 (0.9)	−103.8 ($CFCl_3$)	C, H, F
3,4-(dimethylmethylenedioxy)phenyl	Et	$C_{13}H_{14}F_2O_4$	74	113-115 (1.4)	−102.3 ($CDCl_3$)	C, H, F
1-naphthyl	Et	$C_{14}H_{12}F_2O_2$	77	104-105 (0.3)	−100.4 ($CFCl_3$)	C, H, F
1-naphthyl	CH_3	$C_{13}H_{10}F_2O_2$	76	108-109 (0.7)	−100.6 ($CFCl_3$)	C, H
2-naphthyl	Et	$C_{14}H_{12}F_2O_2$	53	130-133 (1.2)	−100.4 ($CFCl_3$)	C, H, F
3-(1-acetyl)indolyl	Et	$C_{14}H_{13}F_2NO_3$	84	67-68[b]	−100.9 ($CDCl_3$)	C, H, F, N
3-[1-(4-chlorobenzoyl)]indolyl	Et	$C_{19}H_{14}ClF_2NO_3$	82	110-112[c]	−98.3 (Me_2SO-d_6)	C, H, F, N
4-isobutylphenyl	Et	$C_{14}H_{18}F_2O_2$	84	99 (0.5)	−103.5 ($CDCl_3$)	C, H, F

[a] Analyses indicated were within 0.4% of the theoretical value. [b] Melting point when recrystallized from hexane. [c] Melting point when recrystallized from heptane.

Table II. α,α-Difluoroarylacetic Acids ($ArCF_2CO_2H$)

Ar	formula	method	yield, %	recryst solvent	mp, °C	^{19}F NMR, δ (solvent)	anal.[a]
phenyl	$C_8H_6F_2O_2$	B	50	$CFCl_3$	62-63	−105.7 ($CFCl_3$)	C, H, F
4-(trifluoromethyl)phenyl	$C_9H_5F_5O_2$	A	79	$CFCl_3$	94-96	−63.8, −106.5 ($CFCl_3$)	C, H, F
4-(perfluoroisopropyl)phenyl	$C_{11}H_5F_9O_2$	A	97	$CFCl_3$	83-85	−76.1, −182.9, −106.3 ($CFCl_3$)	C, H, F
4-biphenylyl	$C_{14}H_{10}F_2O_2$	A	86	benzene/hexane	131-133	−105.6 ($CDCl_3$)	C, H, F
1-naphthyl	$C_{12}H_8F_2O_2$	A	67	hexane	109-110	−99.8 (Me_2SO-d_6)	C, H, F
2-naphthyl	$C_{12}H_8F_2O_2$	B	70	benzene	138-139	−102.44 (Me_2SO-d_6)	C, H, F
4-isobutylphenyl	$C_{12}H_{14}F_2O_2$	B	97	$CFCl_3$	69-71	−105.2 ($CDCl_3$)	C, H, F

[a] Analyses indicated were within 0.4% of the theoretical value.

Table III. α,α-Difluoroarylacetamides ($ArCF_2CONHR$)

Ar	R	formula	yield, %	recryst solvent	mp, °C	^{19}F NMR, δ (solvent)	anal.[a]
phenyl	H	$C_8H_7F_2NO$	89	benzene	112-114	−103.4 (acetone-d_6)	C, H, F, N
3,4-difluorophenyl	H	$C_8H_5F_4NO$	83	chlorobutane	96-98	−134.1, −136.3, −102.8 ($CDCl_3$)	C, H, F, N
3,4-difluorophenyl	CH_3	$C_9H_7NF_4O$	85	hexane	69-71	−134.2, −136.3, −102.7 ($CDCl_3$)	C, H, N
1-naphthyl	H	$C_{12}H_9F_2NO$	63	heptane	86-88	−99.1 ($CDCl_3$)	C, H, N, F[b]
3,4-(dimethylmethylenedioxy)phenyl	H	$C_{11}H_{11}F_2NO_3$	89	chlorobutane	74-75	−100.5 (Me_2SO-d_6)	C, H, F, N

[a] Analyses indicated were within 0.4% of the theoretical value. [b] Calcd F, 17.18; found F, 16.69.

mixture was broken up and mixed with 200 mL of water. The aqueous mixture was stirred for 15 min, and the suspended solid was collected on a filter, washed with water, and dried in air. Recrystallization from heptane gave 20.03 g (82%) of ethyl 1-(4-chlorobenzoyl)-α,α-difluoro-3-indoleacetate as near-colorless crystals: mp 110–112 °C; IR (KBr) 5.64 (CF_2CO), 5.87 μm (NC=O).

α,α-Difluoroarylacetic Acids (Table II). The α,α-difluoroarylacetic acids listed in Table II were prepared from the corresponding ethyl ester by hydrolysis, under either acid conditions (procedure A) or basic conditions (procedure B). A typical example of each procedure follows.

Procedure A. α,α-Difluoro-2-naphthyleneacetic Acid. A solution of 33.8 g (0.135 mol) of ethyl α,α-difluoro-2-naphthaleneacetate and 30 g (0.135 mol) of 58% hydriodic acid in 225 mL of acetic acid was refluxed for 60 min, then cooled, and poured into 500 mL of ice–water. The solid that precipitated was collected on a filter, washed with water, dried, and recrystallized from hexane to give 18.0 g of colorless crystals.

Procedure B. α,α-Difluoro-4-(2-methylpropyl)benzeneacetic Acid. A mixture of 14.1 g (0.055 mol) of ethyl α,α-difluoro-4-(2-methylpropyl)benzeneacetate and 75 mL of 1 N NaOH was stirred at 25 °C for 18 h and then mixed with 75 mL of 1 N HCl. The reaction mixture was extracted with $CFCl_3$, and the extracts were washed with water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure to give 12.2 g of α,α-difluoro-4-(2-methylpropyl)benzeneacetic acid as white crystals.

α,α-Difluoroarylacetamides (Table III). The α,α-difluoroarylacetamides listed in Table III were prepared by the reaction of the corresponding ethyl ethers with ammonia, as illustrated in the following example.

α,α-Difluoro-3,4-(dimethylmethylenedioxy)benzeneacetamide. A solution of 17.42 g (0.064 mol) of ethyl α,α-difluoro-3,4-(dimethylmethylenedioxy)benzeneacetate in 100 mL of ethanol was saturated with anhydrous ammonia gas at 25 °C and stirred overnight. Evaporation to dryness under reduced pressure gave a residue that was recrystallized from chlorobutane–hexane to give 13.80 g (89%) of α,α-difluoro-3,4-(dimethylmethylenedioxy)benzeneacetamide as colorless needles.

α,α-Difluorobenzeneacetonitrile. A mixture of 11.3 g (0.066 mol) of α,α-difluorobenzeneacetamide and 19 g (0.13 mol) of phosphorus pentoxide was heated strongly in a simple still, first at atmospheric pressure and then at reduced pressure (10 mm), until no further liquid distilled. The distillate was redistilled to

Table IV. Ethyl α-Oxoarylacetates ($ArCOCO_2C_2H_5$)

Ar	formula	yield, %	bp, °C (mm)	anal.[a]
4-(trifluoromethyl)phenyl	$C_{11}H_9F_3O_3$	47	102-104 (3.8)	C, H, F
4-(perfluoroisopropyl)phenyl	$C_{13}H_9F_7O_3$	40	84-85 (0.5)	C, H, F
3,4-difluorophenyl	$C_{10}H_8F_2O_3$	57	135-136 (20)	C, H
3-fluoro-4-methoxyphenyl	$C_{11}H_{11}FO_4$[b]	45	105 (0.3)	C, H, F
1-naphthyl	$C_{14}H_{12}O_3$	80	135-141 (0.6)	C, H
2-naphthyl	$C_{14}H_{12}O_3$	53	130-133 (1.2)	C, H
3,4-(dimethylmethylenedioxy)phenyl	$C_{13}H_{14}O_5$	24	119-123 (0.15)	C, H

[a] Analyses were within 0.4% of calculated values. [b] Prepared by reaction of the arylmagnesium bromide with diethyl oxalate.

give 6.07 g (60%) of α,α-difluorobenzeneacetonitrile as a colorless liquid: bp 94–95 °C (98 mm); ^{19}F NMR (CCl_3F) δ −83.4 (m). Anal. Calcd for $C_8H_5F_2N$: C, 62.74; H, 3.29; F, 24.82; N, 9.15. Found: C, 62.65; H, 3.50; F, 24.79; N, 9.24.

Ethyl α-Oxoarylacetates (Table IV). Most of the new α-keto esters listed in Table IV were prepared from the corresponding bromoaryl compounds, butyllithium, and diethyl oxalate, as illustrated below. In some cases, the α-oxoarylacetates were prepared by reaction of the substituted aryl Grignard reagent and diethyl oxalate.

Ethyl α-Oxo-4-(trifluoromethyl)benzeneacetate. A solution of 0.3 mol of butyllithium in hexane (188 mL) was cooled to −60 °C, and a solution of 67.5 g (0.3 mol) of *p*-bromo(trifluoromethyl)benzene in 200 mL of ether was added dropwise. The reaction mixture was warmed to room temperature and then added dropwise to a solution of 175 g (1.2 mol) of diethyl oxalate in 400 mL of ether cooled to −60 °C. The reaction mixture became very dark green, but the color faded to yellow after warming to room temperature. A 125-mL sample of 10% HCl and then 500 mL of water were added to dissolve the precipitated salts. The organic layer was separated, washed with water, dried ($MgSO_4$), and distilled to give 35.0 g of ethyl α-oxo-4-(trifluoromethyl)-benzeneacetate as a light yellow liquid: IR (liquid) 5.87 and 5.74 μm (C=O); ^{19}F NMR (CCl_3F) δ −63.7 (s).

The pot residue from this distillation was sublimed at 1.2 mm (about 110 °C) to give 8.2 g of light yellow solid. Recrystallization from hexane gave 5.3 g of 4,4′-bis(trifluoromethyl)benzil as light yellow crystals: mp 132–136 °C; ^{19}F NMR (acetone-d_6) δ −63.4; IR (KBr) 5.97 μM (C=O); UV (CH_3CN) λ_{max} 393 nm (ε 58.6), 254 (20 600). Anal. Calcd for $C_{16}H_8F_6O_2$: C, 55.51; H, 2.33; F, 32.92. Found: C, 55.68; H, 2.29; F, 33.51.

Ethyl α-Oxo-3,4-difluorobenzeneacetate. A round-bottom flask containing 1.2 g of magnesium turnings and 15 mL of anhydrous ether was fitted with a dropping funnel containing a solution of 11.04 g (.056 mol) of 3,4-difluorobromobenzene in 15 mL of anhydrous ether. Without stirring, 3–4 mL of the solution in the funnel was added in one portion. A test-tube scale Grignard reaction was started and added to the contents of the flask. Once the reaction started, an additional 10–15 mL of ether was added, and the rest of the 3,4-difluorobromobenzene–ether solution was added dropwise as the reaction refluxed spontaneously at a fast rate.

In a second flask was placed 29.2 g (0.2 mol) of diethyl oxalate in 30 mL of ether and the solution was cooled to −50 °C. The contents of the first flask were then added to the diethyl oxalate in small portions through a layer of glass wool to filter any unreacted Mg metal. The temperature rose quickly 10–20 °C and was controlled by cooling and rate of addition. The reaction mixture was allowed to warm to room temperature and then mixed slowly with 50 mL of 5% HCl. The now clear and yellowish organic layer was separated, washed with water, dried, and distilled to give 6.75 g of ethyl α-oxo-3,4-difluorobenzeneacetate.

Ethyl 1-Acetyl-α-oxo-3-indoleacetate. A mixture of 79.64 g (0.37 mol) of ethyl α-oxo-3-indoleacetate[4] in 250 mL of acetic anhydride was refluxed for 4 h, then cooled, and mixed with 1.2 L of water. The mixture was stirred until a solid formed. This solid was collected on a filter, washed with water, and recrystallized from ethanol to give 89.1 g (93%) of ethyl 1-acetyl-α-oxo-3-indoleacetate as light yellow crystals: mp 94–96 °C; ^1H NMR (Me_2SO-d_6) consistent. Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.71; H, 4.98; N, 5.47.

Ethyl 1-(4-Chlorobenzoyl)-α-oxo-3-indoleacetate. *p*-Chlorobenzyl chloride, 17.5 g (0.1 mol), was added to a solution of 21.72 g (0.1 mol) of ethyl α-oxo-3-indoleacetate in 200 mL of pyridine. The reaction mixture was refluxed for 3 h, then cooled, and poured into 1 L of water. The solid precipitate was collected on a filter, washed with water, and recrystallized from ethanol to give 27.1 g (76%) of ethyl 1-(4-chlorobenzoyl)-α-oxo-3-indoleacetate as colorless plates, mp 132–134 °C. Anal. Calcd for $C_{19}H_{14}ClNO_4$: C, 64.14; H, 3.97; Cl, 9.97; N, 3.94. Found: C, 64.40; H, 3.83; Cl, 10.01; N, 4.26.

2,2-Difluoro-2-(3,4-difluorophenyl)ethylamine Hydrochloride. A 6-mL sample of borane methyl sulfide was added dropwise to a solution of 5.0 g (0.024 mol) of α,α-difluoro-3,4-difluorobenzeneacetamide (Table III) in 25 mL of tetrahydrofuran at room temperature. The mixture was stirred overnight, then refluxed for 2 h, and cooled. Methanol (15 mL) was added dropwise, and then the reaction mixture was saturated with anhydrous HCl, allowed to stand overnight, refluxed for 0.5 h, and cooled. The solid product was collected on a filter and washed with a minimum amount of cold methanol to give 1.35 g (25%) of 2,2-difluoro-2-(3,4-difluorophenyl)ethylamine hydrochloride as white crystals: mp 212–214 °C; ^1H NMR (Me_2SO-d_6) δ 3.78 (t, 17 Hz, 8 H), 8.5 (br NH_2), 7.0–8.0 (m, 8 H); ^{19}F NMR (Me_2SO-d_6) δ −134.7 (m, 1 F; ^1H-decoupled d, t, J_{FF} = 21, 2.5 Hz), −136.7 (m, 1 F; ^1H-decoupled d, J_{FF} = 21 Hz), −97.5 (t, J_{FF} = 2.5 Hz, 2 F).

3,3-Difluoro-1,3-dihydro-1-methyl-2*H*-indol-2-one. A mixture of 8.06 g (0.05 mol) of 1-methylisatin and 12.6 mL (0.1 mol) of DAST was warmed gently to 60 °C and held there for 15 min, during which time the solid went into solution. An exotherm was observed, and some cooling was needed to maintain the temperature at 60 °C. The reaction mixture was cooled and poured over ice. The solid that formed was collected on a filter, washed with water, and dried in air. Recrystallization from heptane gave 8.70 g (95%) of 3,3-difluoro-1,3-dihydro-1-methyl-2*H*-indol-2-one as yellow crystals: mp 90–92 °C; IR (KBr) 5.70 μm; ^{19}F NMR ($CDCl_3$) δ −112.8 (m); ^1H NMR ($CDCl_3$) δ 3.17 (s, 3 H), 6.7–7.7 (m, 4 H). Anal. Calcd for $C_9H_7F_2NO$: C, 59.01; H, 3.85; F, 20.75; N, 7.65. Found: C, 59.33; H, 3.92; F, 20.87; N, 7.54.

Registry No. 1, 1603-79-8; 2, 2248-46-6; 3, 2058-74-4; 4, 73789-91-0; 5, 73789-92-1; 8a, 73789-93-2; 9a, 73789-94-3; methyl α,α-difluorobenzeneacetate, 56071-96-6; ethyl α,α,3,4-tetrafluorobenzeneacetate, 73789-95-4; ethyl α,α-difluoro-4-(trifluoromethyl)benzeneacetate, 73789-96-5; ethyl α,α-difluoro-4-(perfluoroisopropyl)-benzeneacetate, 73789-97-6; ethyl α,α-difluoro-4-phenylbenzeneacetate, 73789-98-7; ethyl α,α-difluoro-3,4-(dimethylmethylenedioxy)benzeneacetate, 73789-99-8; ethyl α,α-difluoro-1-naphthaleneacetate, 73790-00-8; methyl α,α-difluoro-1-naphthaleneacetate, 73790-01-9; ethyl α,α-difluoro-2-naphthaleneacetate, 73790-02-0; ethyl 1-(4-chlorobenzoyl)-α,α-difluoro-3-indoleacetate, 73790-03-1; ethyl α,α-difluoro-4-isobutylbenzeneacetate, 73790-04-2; methyl α-oxobenzeneacetate, 15206-55-0; ethyl 3,4-difluoro-α-oxobenzeneacetate, 73790-05-3; ethyl α-oxo-4-(trifluoromethyl)benzeneacetate, 73790-06-4; ethyl α-oxo-4-(perfluoroisopropyl)benzeneacetate, 73790-07-5; ethyl α-oxo-4-phenylbenzeneacetate, 6244-53-7; ethyl 3,4-(dimethylmethylenedioxy)-α-oxobenzeneacetate, 73790-08-6; ethyl α-oxo-1-naphthaleneacetate, 33656-65-4; methyl α-oxo-1-naphthaleneacetate, 16738-12-8; ethyl α-oxo-2-naphthaleneacetate, 73790-09-7; ethyl 1-acetyl-α-oxo-3-indoleacetate, 65047-16-7; ethyl 1-(4-chlorobenzoyl)-α-oxo-3-indoleacetate, 73790-10-0; ethyl 4-isobutyl-α-oxobenzeneacetate, 60473-28-1; α,α-difluorobenzeneacetic

(4) Shaw, K. N. F.; McMillan, A.; Gudmundson, A. G.; Armstrong, M. D. *J. Org. Chem.* **1958**, *23*, 1171.

acid, 360-03-2; α,α-difluoro-4-(trifluoromethyl)benzeneacetic acid, 73790-11-1; α,α-difluoro-4-(perfluoroisopropyl)benzeneacetic acid, 73790-12-2; α,α-difluoro-4-phenylbenzeneacetic acid, 73790-13-3; α,α-difluoro-1-naphthaleneacetic acid, 73790-14-4; α,α-difluorobenzeneacetamide, 383-19-7; α,α,3,4-tetrafluorobenzeneacetamide, 73790-15-5; *N*-methyl-α,α,3,4-tetrafluorobenzeneacetamide, 73790-16-6; α,α-difluoro-1-naphthaleneacetamide, 73790-17-7; α,α-difluoro-3,4-(dimethylmethylenedioxy)benzeneacetamide, 73790-18-8; *p*-bromo(trifluoromethyl)benzene, 402-43-7; *p*-bromo(perfluoroisopropyl)benzene, 2396-23-8; 3,4-difluorobromobenzene, 348-61-8; 1-bromo-3-fluoro-4-methoxybenzene, 2357-52-0; 1-bromonaphthalene, 90-11-9; 2-bromonaphthalene, 580-13-2; 1-bromo-3,4-(dimethylmethylenedioxy)benzene, 73790-19-9; ethyl α-oxo-3,4-difluorobenzeneacetate, 345-72-2; DAST, 38078-09-0; α,α-difluorobenzeneacetonitrile, 2002-72-4; diethyl oxalate, 95-92-1; 4,4′-bis(trifluoromethyl)benzil, 73790-20-2; ethyl α-oxo-3-indoleacetate, 51079-10-8; *p*-chlorobenzyl chloride, 104-83-6; 2,2-difluoro-2-(3,4-difluorophenyl)ethylamine hydrochloride, 73790-21-3.

Trifluoroperacetic Acid. Oxidation of Aromatic Rings

R. Liotta* and W. S. Hoff

Corporate Research Science Laboratories, Exxon Research and Engineering Co., Linden, New Jersey 07036

Received February 26, 1980

Trifluoroperacetic acid is an oxidizing reagent capable of converting alkylbenzenes to the corresponding aliphatic carboxylic acids. No trace of aromatic carboxylic acid is ever observed. Aromatic heterocyclic compounds do not behave like their hydrocarbon analogues. Quinoline and pyridine are oxidized to the corresponding *N*-oxides, and dibenzothiophene is oxidized to the sulfone. No destruction of the ring is found in these latter three cases. The reaction mixture of hydrogen peroxide and trifluoroacetic acid undergoes a decomposition reaction to form carbon dioxide and fluoroform. The rate of this decomposition is slow compared to the oxidation so that it does not interfere with the primary reaction process. However, attempts to quantify the amount of aromatic carbons in a compound or mixture of compounds must be done with caution.

Recently, Deno described some interesting degradation work[1] which utilized trifluoroperacetic acid. Reagents of this type[2] are known to be a source of positive hydroxyl groups which electrophilically attack certain aromatic rings. This process is believed to proceed through various progressive hydroxylations until the ring is destroyed. If an aliphatic side chain were present, an aliphatic carboxylic acid would be produced. For example, *n*-propylbenzene, upon oxidation with trifluoroperacetic acid, produced butyric acid in good yields. Deno performed this oxidation on numerous other hydrocarbons, and in each case the major product formed was derived from the destruction of the aromatic moiety, with the aliphatic portion of the molecule surviving the oxidation. In all of this work there was also produced a significant amount of minor products which the authors left unidentified. Some quantity of acetic acid was usually produced but the amount of this product was diminished by the addition of sulfuric acid to the reaction mixture at the start of the reaction.[3] In the earlier work[1] the composition was analyzed after distillation of volatile material to obtain a concentrated solution for ^{1}H NMR analysis. Accordingly, volatile or minor products (<5%) would not be observed. The existence of these minor products (sometimes totaling 30–40% of the observed products) sparked our curiosity as to their identity. Several of the published oxidations were repeated and extended to other structures; the product mixtures were analyzed by gas chromatography/mass spectroscopy (GC/MS) under conditions which are known to separate the expected products.

It has been suggested[1,3] that this oxidative degradation should be used to identify and quantify aliphatic side chains on coal and similar materials. Unfortunately, the behavior of some structural types in this reaction is not known, namely, aromatic amines and sulfur compounds which are known to be present in coal. Part of this study fills this gap. Furthermore, no mention of gas evolution was made in the previous studies, and, therefore, material balances could not be calculated. The gases evolved during the reaction have now been identified. The GC analysis also served to quantify the relative abundances of nonvolatile products. For the elucidation of the mechanistic details of the reaction, a partial-oxidation study was performed. During the course of these partial oxidations, reaction intermediates were observed (by mass spectroscopy) and most of them identified.

Results and Discussion

Instability of Reaction Mixture. All of the off gases were allowed to pass through a barium hydroxide scrubber solution. More carbon dioxide was produced in certain reactions than was possible from the amount of organic substrate present. The carbon dioxide produced was collected as barium carbonate and weighed after thorough drying. The barium carbonate was then decomposed with hot concentrated HCl to liberate CO_2. The measured quantity of CO_2 (an ascarite trap) was consistent with that expected for pure barium carbonate. It was hypothesized that the oxidizing reagent was decarboxylating according to eq 1. To test this, we ran a blank (no organic substrate);

$$CF_3CO_2H \xrightarrow{H_2O_2} CHF_3 + CO_2 \qquad (1)$$

indeed, CO_2 slowly evolved. Further, we found that the decomposition of trifluoroacetic acid–hydrogen peroxide (TFA/H_2O_2) reagent was catalyzed by certain materials. For example, in one experiment addition of a small crystal of cuprous chloride to the standard oxidizing reagent

(1) N. C. Deno, B. A. Greigger, L. A. Messner, M. D. Meyer, and S. G. Stroud, *Tetrahedron Lett.* 1703, (1977).
(2) (a) H. Hart, *Acc. Chem. Res.*, **4**, 377 (1971); (b) H. Hart and R. M. Lange, *J. Org. Chem.*, **31**, 3776 (1966); (c) M. E. Kurz and P. Kovacic, *J. Am. Chem. Soc.*, **89**, 4960 (1967); (d) J. A. Vesely and L. Schmerling, *J. Org. Chem.*, **35**, 4028 (1970).
(3) N. C. Deno, B. A. Greigger, and S. G. Stroud, *Fuel*, **57**(8) 455 (1978).

0022-3263/80/1945-2887$01.00/0