Kirk-Othmer Encyclopedia of Chemical Technology.

FLUORINATED AROMATIC COMPOUNDS

Aromatic fluorine compounds have been known for nearly a century, but numerous applications have surfaced only in recent years. The special properties conferred by fluorine justify the higher costs required to produce fluoroaromatics. The unusual physiochemical and biological properties that fluorine imparts to aromatics result from the small size of fluorine (it is bioisosteric with both the hydrogen atom and the hydroxyl group) and from its striking electronic properties, including high electronegativity and the ability to alter polarity of adjacent groups, as well as to donate electrons by resonance. Other significant properties are the enhanced stability of the C–F bond in the absence of activating groups, high lipid solubility, hydrogen-bonding potential (acceptor role), and enzyme inhibition. The carbon–fluorine link in fluoroaromatics has been of considerable value as a label for metabolic, mechanistic, and structural studies.

Depending on which substituents are present, fluoroaromatic intermediates can be converted into fluorinated or fluorine-free products. Fluorine substitution can affect the biological spectrum of the parent aromatic or heterocyclic compound by enhancement of desired properties or by suppression of undesired properties. Fluorine-containing aromatics have been incorporated into drugs (hypnotics, tranquilizers, antiinflammatory agents, analgesics, antibacterials, etc) and into crop protection chemicals (herbicides, insecticides, fungicides). Liquid crystals, positron emission tomography, and imaging systems are newer use areas for fluoroaromatics and fluoroheterocyclics.

For fluorine-free products, the lability of fluorine in fluoronitrobenzenes and other activated molecules permits it to serve as a handle in hair-dye manufacturing operations, high performance polymers such as polyetheretherketone (PEEK), production of drugs such as diuretics, and fiber-reactive dyes. Labile fluorine has also been used in analytical applications and biological diagnostic reagents.

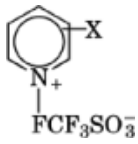
1. Preparative Methods

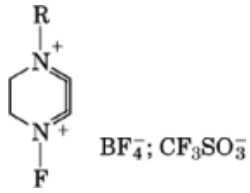
1.1. Ring-Fluorinated Aromatics and Heterocyclics

In contrast with other molecular halogens (Cl_2, Br_2), early attempts at direct aromatic substitution with fluorine (F_2) gave violent reactions involving ring scission, addition, coupling, and polymerization. Consequently, indirect fluorination techniques based on diazotization of anilines or exchange fluorination of activated haloaromatics were developed. Recent advances in synthetic methods include discoveries of new fluorinating agents and modifications of known methods. Some of these efforts were stimulated by objectives to effect selective fluorination of natural or biologically active compounds. The need to prepare ^{18}F-labeled pharmaceuticals for use in positron emission tomography also accelerated the need for improved aromatic fluorination techniques (1).

1.1.1. Substitutive Aromatic Fluorination

The search for improved substitutive aromatic fluorination tools based on tamed fluorine continues (2). These reagents include elemental fluorine (F_2) (3–7), chlorine trifluoride (8) and pentafluoride (9), xenon fluorides (eg, XeF_2) (10), silver difluoride (11), cesium fluoroxysulfate (12), trifluoromethyl hypofluorite (CF_3OF) (13), bis(fluoroxy)difluoromethane ($CF_2(OF)_2$) (13), and acetyl hypofluorite (CH_3CO_2F) (14, 15). Substitutive aromatic fluorination with elemental fluorine is commercially practiced for the manufacture of the antineoplastic, 5-fluorouracil (5-FU) from uracil. Nitrogen–fluorine reagents can also effect substitutive aromatic fluorination, for example, *N*-fluorobis[(trifluoromethyl)sulfonyl]imide (16); *N*-fluorobenzenesulfonimides (NFSi) (17); *N*-fluoropyridinium trifluoromethanesulfonates (18); and 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2·2·2]octane salts, marketed as SELECTOFLUOR reagents (19, 20).



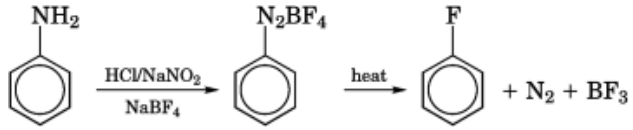


1.1.2. Diazotization Routes

Conventional Sandmeyer reaction conditions are not suitable to make fluoroaromatics. Phenols primarily result from high solvation of fluoride ion in aqueous media.

Fluoroaromatics are produced on an industrial scale by diazotization of substituted anilines with sodium nitrite or other nitrosating agents in anhydrous hydrogen fluoride, followed by *in situ* decomposition (fluorodediazoniation) of the aryldiazonium fluoride (21). The decomposition temperature depends on the stability of the diazonium fluoride (22, 23). A significant development was the addition of pyridine (24), tertiary amines (25), and ammonium fluoride (or bifluoride) (26, 27) to permit higher decomposition temperatures ($>50^\circ C$) under atmospheric pressure with minimum hydrogen fluoride loss.

The Balz-Schiemann reaction is a useful laboratory and industrial method for the preparation of fluoroaromatics. The water-insoluble diazonium fluoroborate is filtered, dried, and thermally decomposed to give the aryl fluoride, nitrogen, and boron trifluoride (28–30).



Extreme caution must be exercised in the handling of nitroaryldiazonium fluoroborates because of unruly decomposition (29, 30). Water-insoluble aryl diazonium hexafluorophosphates, ArN_2PF_6, frequently give higher yields of the fluoroaromatic (31). Substitution of aqueous sodium nitrite by nitrite esters–boron trifluoride in organic solvents gives high yields of aryl diazonium fluoroborate (32, 33). A variant of the Balz-Schiemann reaction features diazotization by nitrosonium tetrafluoroborate, $NO^+BF^-_4$, in organic solvents followed by *in situ* decomposition to give high yields of aryl fluoride (34). A single fluorine atom can be introduced

sequentially by the Balz-Schiemann reaction (via successive nitration, reduction, and diazotization) for a total of up to four fluorine atoms, eg, 1,2,4,5-tetrafluorobenzene. The Balz-Schiemann process is used to manufacture fluoroaromatics, eg, *o*- and *p*-difluorobenzene, not readily accessible by standard aniline–hydrogen fluoride diazotization or exchange-fluorination (Halex) routes. Estimates of producer capacities utilizing Balz-Schiemann technology range from 50–100 t/yr (35) to hundreds of t/yr (36). A continuous feed aryl diazonium fluoroborate decomposition step has been patented (37) and commercial details described (38).

The discovery of the Balz-Schiemann reaction in 1927 replaced the earlier Wallach procedure (1886) based on fluorodediazoniation of arenediazonium piperidides (aryltriazenes) in aqueous hydrogen fluoride (39, 40). The Wallach aryltriazene fluorodediazoniation technique has found new utility in agrochemicals (41), pharmaceuticals (42), and positron emission tomography (43). This is illustrated in the synthesis of 2,4-dichloro-5-fluorotoluene [86522-86-3], an intermediate to the fluoroquinolone antibacterial ciprofloxacin, by heating *N*-(2,4-dichloro-5-methylphenyl)-*N*′,*N*′-dimethyltriazene in anhydrous fluoride (42).

1.1.3. Exchange Fluorination

Fluorobenzene cannot be made from chlorobenzene and potassium fluoride because of absence of substrate activation. The halogen exchange (Halex) reaction of activated haloaromatics and haloheterocyclics with potassium fluoride is a primary industrial fluoroaromatics synthesis tool (44, 45). Early work featured preparation of *o*- and *p*-fluoroaromatics activated by nitro or cyano groups by exchange fluorination in dipolar aprotic solvents (46). Features of this technique include good fluorine utilization (1:1 stoichiometry), facile product separation, and potential recycling of potassium chloride (as KF) by treatment with hydrogen fluoride or fluorine. Aprotic solvents permit less solvation of fluoride ion (as compared with protic solvents), a kinetically significant amount of fluoride ion in solution, and greater insolubility of potassium chloride which, in turn, provides a further reaction driving force.

$$p-\mathrm{ClC_6H_4NO_2} + \mathrm{KF} \overset{\text{solvent}}{\Rightarrow} p-\mathrm{FC_6H_4NO_2}$$

The degree of fluorination can be limited by the thermal stability of the solvent or by its reaction with basic potassium fluoride through proton abstraction. Such solvent-derived by-products can subsequently react with the starting material and/or main product.

Of the alkali metal fluorides, potassium fluoride offers the best compromise between cost and effectiveness. Although cesium fluoride generally gives higher yields, its higher cost may be a potential drawback as an industrial fluorination tool except for those substrates resistant to potassium fluoride. In contrast, inexpensive sodium fluoride consistently gives lower yields than potassium fluoride. Tetra-*n*-butylammonium fluoride (TBAF) (47), tetra-*n*-butylphosphonium hydrogen difluoride, and dihydrogen trifluoride (48) have been successfully employed in Halex reactions. Mode of potassium fluoride preparation (spray-, calcine- or freeze-dried) can affect exchange fluorination activity (49, 50). Enhanced fluorination rates are associated with decreasing particle size and increasing surface area.

Halex rates can also be increased by phase-transfer catalysts (PTC) with widely varying structures: quaternary ammonium salts (51–53); 18-crown-6-ether (54); pyridinium salts (55); quaternary phosphonium salts (56); and poly(ethylene glycol)s (57). Catalytic quantities of cesium fluoride also enhance Halex reactions (58).

The inertness of chlorine in the meta position in Halex reactions is of commercial value. For example, 3,4-dichloronitrobenzene [99-54-7] forms 3-chloro-4-fluoronitrobenzene [350-30-1], which is then reduced to 3-chloro-4-fluoroaniline [367-21-5] for incorporation in the herbicide flamprop–isopropyl or the fluoroquinolone antibacterials, norfloxacin and pefloxacin.

Activating groups other than nitro or cyano have extended the versatility of exchange-fluorination reactions: —CHO (59, 60); —COCl (60); $-CO_2R$ (61); —CONRCO— (62); $-SO_2Cl$ (63); and $-CF_3$ (56, 64).

Explosions have been reported during preparation of fluoronitroaromatics by the Halex reaction on a laboratory or industrial scale: *o*-fluoronitrobenzene (65); 2,4-dinitrofluorobenzene (66); 2,4-difluoronitrobenzene (67); and 1,5-difluoro-2,4-dinitrobenzene (68).

Fluorodenitration of nitroaromatics represents an exchange fluorination technique with commercial potential. For example, *m*-fluoronitrobenzene [402-67-5] from *m*-dinitrobenzene [99-65-0] and KF in the presence of various promoters can be realized (69–72). This is not feasible under Halex conditions with *m*-chloronitrobenzene [121-73-3].

1.1.4. Saturation–Rearomatization

The first commercial route to perfluorinated aromatics such as hexafluorobenzene, octafluorotoluene [434-64-0] and fused-ring polycyclics was based on a multistage saturation–rearomatization process (73). In the first stage, benzene is fluorinated by a high valency oxidative metal fluoride (cobalt trifluoride) to give a mixture of polyfluorocyclohexanes. The latter is subjected to a combination of dehydrofluorination (with alkali) and/or defluorination (with heated iron, iron oxide, or nickel packing) to give hexa-, penta-, and tetrafluorobenzenes. Modifications of the first stage include the use of complex metal fluorides, eg, potassium tetrafluorocobaltate(III), that have been found to be milder and more selective fluorinating agents than cobalt trifluoride (74). A related process features successive treatment of hexachlorobenzene with chlorine trifluoride (75) or fluorine (76), followed by dehalogenation with iron powder at 300°C. More emphasis is now given to Halex processes for perfluoroaromatics manufacture rather than saturation–rearomatization routes.

1.1.5. Fluoroaliphatic Thermolytic Routes

The reaction of difluorocarbene (generated from $CHClF_2$ at 600°C) with cyclopentadiene to give fluorobenzene (70% yield) has been scaled up in a pilot-plant/semiworks facility (capacity = several dozen t/yr) (77, 78). The same process can now be effected under liquid-phase conditions in the presence of phase-transfer catalysts (79, 80).

1.1.6. Miscellaneous Methods

Exhaustive evaluation of the decarbonylation of benzoyl fluorides, ArCOF, by Wilkinson's catalyst [14694-95-2], $Rh[(C_6H_5)_3P]_3Cl$, to give aryl fluorides has established (81) that previous claims (82) cannot be reproduced.

One approach to aryl fluorides (83) based on phenolic derivatives features more moderate thermal decarboxylation of phenyl fluoroformates employing alumina-impregnated platinum group catalysts (84). Treatment of phenyl chloroformates with hydrogen fluoride using Lewis acid catalysts to give aryl fluorides may have potential industrial importance (85, 86).

Fluorodesulfonylation represents a complementary extrusion technique to aryl fluorides (87) which has attracted interest (88, 89). For example, 2-fluorobenzonitrile [394-47-8] was obtained in 84% yield from 2-cyanobenzenesulfonyl fluoride and potassium fluoride in sulfolane (88).

The electrochemical route to fluoroaromatics (90) based on controlled potential electrolysis in the absence of hydrogen fluoride (platinum anode, $+2.4$ V; acetonitrile solvent; tetraalkylammonium fluoride electrolyte) has not been commercialized. However, considerable industrial interest in the electrochemical approach still exists (91–93).

The single-step *p*-fluoroaniline [31-40-4] process based on fluorodeoxygenation of nitrobenzene (via *in situ* generation of *N*-phenylhydroxylamine) in anhydrous hydrogen fluoride (94–96) has not been commercialized primarily due to concurrent formation of aniline, as well as limited catalyst life. The potential attractiveness of this approach is evidenced by numerous patents (97–101). Concurrent interest has been shown in the two-step process based on *N*-phenylhydroxylamine (HF-Bamberger reaction) (102–104).

1.2. Side-Chain Fluorinated Aromatics and Heterocyclics

Benzotrifluorides generally are prepared from trichloromethylaromatics with metal fluorides or hydrogen fluoride. Industrial processes feature reaction with hydrogen fluoride under high pressure, atmospheric pressure, or vapor-phase conditions. A potential simplification is the single-step conversion of toluene to benzotrifluoride employing chlorine–hydrogen fluoride (CCl_4 diluent, 460°C) (105).

1.3. Sulfur Tetrafluoride and Aromatic Carboxylic Acids

Benzotrifluorides also are prepared from aromatic carboxylic acids and their derivatives with sulfur tetrafluoride (SF_4) (106, 107). Hydrogen fluoride is frequently used as a catalyst. Two equivalents of sulfur tetrafluoride are required:

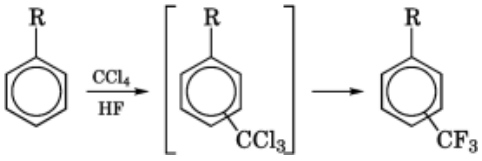
$$ArCOOH + SF_4 \xrightarrow{HF} ArCOF + HF + SOF_2$$

$$ArCOF + SF_4 \longrightarrow ArCF_3 + SOF_2$$

The high cost of SF_4 and the incomplete use of fluorine justify its use only for inaccessible benzotrifluorides. The related liquid S–F reagent, (diethylamino)sulfur trifluoride (DAST), $(C_2H_5)_2NSF_3$, also effects similar transformations with aromatic carboxylic acids (108).

1.4. Perfluoroalkylation

A significant technical advance features perfluoroalkylation of aromatics (devoid of electron-withdrawing groups) with carbon tetrachloride–hydrogen fluoride to give high selectivity of benzotrifluorides (109, 110). Hydrogen fluoride performs a threefold role: solvent, Friedel-Crafts alkylation catalyst, and fluorinating agent.



Aromatic perfluoroalkylation can be effected by fluorinated aliphatics via different techniques. One category features copper-assisted coupling of aryl halides with perfluoroalkyl iodides (eg, CF_3I) (111, 112) or difluoromethane derivatives such as CF_2Br_2 (Burton's reagent) (113, 114), as well as electrochemical trifluoromethylation using CF_3Br with a sacrificial copper anode (115). Extrusion of spacer groups attached to the fluoroalkyl moiety, eg, CF_3COONa and higher perfluorocarboxylated salts (116, 117), CF_3SO_2Na (118), and esters such as $CF_2ClCOOCH_3$ (119) or $FSO_2CF_2COOCH_3$ (120), represents a novel trifluoromethylation concept.

$$ArI + CF_3COONa \xrightarrow{CuI/NMP} Ar—CF_3$$

Aromatic perfluoroalkylation can also be performed in the absence of copper employing $(CF_3COO)_2$ (121) or $R_fI(C_6H_5)OSO_2CF_3$ (FITS reagents) (122). Aluminum chloride-catalyzed alkylation of fluorobenzene with hexafluoroacetone, CF_3COCF_3, gave 66% yield of *p*-fluoro-α,α-bis(trifluoromethyl)benzyl alcohol [2402-74-6] (123).

1.4.1. Oxidative Fluorination of Aromatic Hydrocarbons

The economically attractive oxidative fluorination of side chains in aromatic hydrocarbons with lead dioxide or nickel dioxide in liquid HF stops at the benzal fluoride stage (67% yield) (124).

$$p - CH_3C_6H_4NO_2 \xrightarrow{PbO_2/HF} p - CHF_2C_6H_4NO_2$$

1.4.2. Cyclization

Construction of benzotrifluorides from aliphatic feedstocks represents a new technique with economic potential. For example, 1,1,1-trichloro-2,2,2-trifluoroethane [354-58-5] and dimethyl itaconate [617-52-7] form 4-methoxy-6-trifluoromethyl-2*H*-pyran-2-one [101640-70-4], which is converted to methyl 3-(trifluoromethyl)benzoate [2557-13-3] with acetylene or norbornadiene (125).

2. Ring-Fluorinated Benzenes

2.1. Fluorobenzene

2.2. Properties

Fluorobenzene [462-06-6] (monofluorobenzene), C_6H_5F, has a molecular weight of 96.1, and is a colorless mobile liquid with a pleasant aromatic odor (Table 1). Its thermal stability is of a high order; fluorobenzene undergoes no detectable decomposition when kept at 350°C for 24 h at pressures of up to 40.5 MPa (400 atm). Toxicity: oral (rat), $LD_{50} > 4$ g/kg; inhalation (mouse), LD_{50} 45 g/m^3 (2 h) (127).

2.3. Reactions

2.3.1. Electrophilic Substitution

Fluorobenzene electrophilic substitution reactions are more para directing than are the same chlorobenzene reactions (128). Nitration of fluorobenzene with concentrated nitric and sulfuric acid gives a 92:8 mixture of *p*- and *o*-fluoronitrobenzene [1493-27-2] which can be separated by distillation. The other commercial route to *o*- and *p*-fluoronitrobenzene [350-46-9] is based on exchange fluorination (KF) in a polar solvent; phase-transfer catalysts are frequently employed.

The Friedel-Crafts ketone synthesis is of commercial importance in upgrading fluorobenzene for drug, polymer, and electronic applications (Table 2).

2.3.2. Nucleophilic Displacement Reactions

The presence of activating groups, eg, *o, p* nitro groups, makes aromatic fluorine reactive in nucleophilic displacement reactions. This has been demonstrated by determination of the relative fluorine–chlorine displacement ratios from the reaction of halonitrobenzenes with sodium methoxide in methanol (137); F is displaced 200–300 times more readily than Cl.

Numerous applications have been developed based on the lability of fluoronitroaromatics; 4-fluoro-3-nitroaniline [364-76-1] and 4-fluoro-3-nitro-*N,N*-bis(hydroxyethyl)aniline [29705-38-2], commercial hair dye intermediates (138–140); 2,4-dinitrofluorobenzene [70-34-8] (Sanger's reagent), for amino acid characterization (141); 4-fluoro-3-nitrophenyltrimethylammonium iodide [39508-27-5], a protein solubilizing reagent (142); and 4-fluoro-3-nitrophenylazide [28166-06-5], an antibody tagging reagent (143) also used for industrial immobilization of enzymes (144). Other examples of biochemical applications (amino acid or peptide characterization, protein cross-linking reagent) include 2,4-dinitro-5-fluoroaniline [361-81-7] (Bergmann's reagent) (145); 4-fluoro-3-nitrobenzoates (146, 147); 4-fluoro-3-nitrobenzenesulfonic acid [349-05-3] (148); 4-fluoro-3-nitrophenyl

Table 1. Physical Properties of Fluorobenzene

Property	Value
melting point, °C	−42.22
boiling point, °C	84.73
density, 25°C, g/mL	1.0183
coefficient of expansion	0.00116
refractive index, n_D^{25}	1.4629
viscosity, mPa·s(= cP)	
9.3°C	0.653
19.9°C	0.585
80.9°C	0.325
surface tension, mN/m(=dyn/cm)	
9.3°C	28.49
20.0°C	27.71
34.5°C	25.15
latent heat of fusion, J/mol[a]	11,305.2
latent heat of vaporization, 25°C, J/mol[a]	34,576.6
specific heat, 25°C, J/mol[a]	146.3
critical temperature, °C	286.94
critical pressure, kPa[b]	4550.9
critical density, g/mL	0.269
dielectric constant, 30°C	5.42
dipole moment, C·m[c]	4.90×10^{-30}
heat of combustion, J/g[a]	−32, 273.3
heat of formation, kJ/mol[a]	
vapor	−110.5
liquid	−145.2
solubility in water, 30°C, g/100 g	0.154
solubility of water in fluorobenzene, 25°C, g/100 g	0.031
boiling point of binary azeotrope, °C	
with 31 wt % *tert*-butyl alcohol	76.0
with 32 wt % methanol	59.7
with 30 wt % isopropyl alcohol	74.5
flash point (Tag open cup), °C[d]	−13
vapor pressure, in °C and kPa[b]	Antoine equation[e]

[a] To convert J to cal, divide by 4.184.
[b] To convert kPa to mm Hg, multiply by 7.5; $\log \text{kPa} = \log \text{mm Hg} - 0.895$.
[c] To convert C·m to debye (D), divide by 3.336×10^{-30}.
[d] Ref. 126.

[e] $\text{Log}_{10} P = 6.07687 - \dfrac{1248.083}{(t + 221.827)}$.

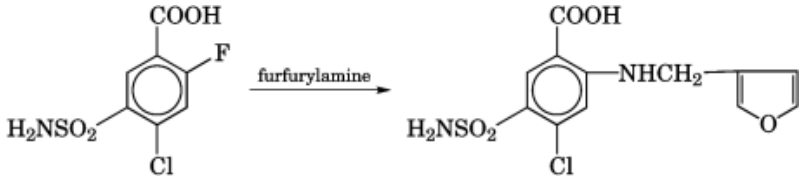
sulfone [51451-34-4] (149); 1,5-difluoro-2,4-dinitrobenzene [327-92-4] (150); 3,5-dinitro-2-fluoroaniline [18646-02-1] (151); 4-fluoro-7-nitrobenzofurazan [29270-56-2] (NBD-F) (152); and 1-fluoro-2,4-dinitrophenyl-5-L-alanine amide [95713-52-3] (Marfey's reagent) (153). Labile fluorine in 4-fluoronitrobenzene can be used to form piperidinylimino-linked polar chromophores for nonlinear optical (NLO) materials (154).

Examples of commercial reactive fluoroaromatics are not restricted to fluoronitrobenzenes. The fluorine-free diuretic, furosemide [54-31-9], is prepared in 85% yield from 2-fluoro-4-chloro-5-sulfamoylbenzoic acid and furfurylamine at 95°C for 2 h (155).

Table 2. Friedel-Crafts Ketone Synthesis with Fluorobenzene[a]

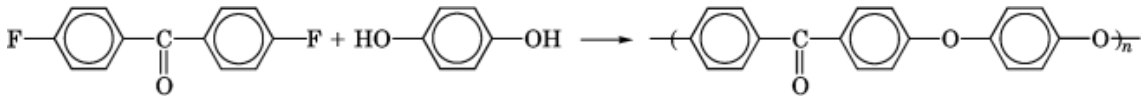
Acylating agent	Reference	Product	CAS Registry Number	End use
4-chlorobutyryl chloride	129	4-chloro-4′-fluorobutyr-ophenone	[3874-54-2]	haloperidol[b] (tranquilizer)
acetyl chloride or acetic anhydride	130	4-fluoroacetophenone	[403-42-9]	flazalone[b] (anti-inflammatory)
4-fluorobenzoyl chloride	131	4,4′-difluorobenzo-phenone	[345-92-6]	polyetheretherketone (PEEK), a high performance ther-moplastic
isophthaloyl chloride	132, 133	1,3-bis(4-fluorobenz-oyl)benzene	[108464-88-6]	poly(arylene ethers) (PAE); polyimides
oxalyl chloride	134	4-fluorobenzoyl chloride	[403-43-0]	liquid crystal inter-mediate
chloroacetyl chloride	135	2-chloro-4′-fluoroaceto-phenone	[456-04-2]	flutriafol[c] (fungicide)
2,3-naphthalenedicar-boxylic anhydride	136	3-(4-fluorobenzoyl)-2-naphthalenecarbox-ylic acid	[91786-16-2]	organo-selenium metallic conductors

[a] $AlCl_3$ catalyst.
[b] See Table 4.
[c] See Table 3.



Cyclothiazide [2259-96-3] is another example of a fluorine-free pharmaceutical (diuretic, antihypertensive) based on *m*-chlorofluorobenzene [625-98-9] where fluorine activation is subsequently provided by two sulfonamide groups (156).

Another commercial application of nucleophilic reactions of nitro-free fluoroaromatics is the manufacture of polyetheretherketone (PEEK) high performance polymers from 4,4′-difluorobenzophenone [345-92-6], and hydroquinone [121-31-9] (131) (see Polyethers, aromatic).



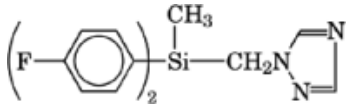
Polyether sulfones (PES) prepared from 4,4′-difluorodiphenyl sulfone and bisphenol A (potassium salt, DMSO) react faster than the corresponding reaction with 4,4′-dichlorodiphenyl sulfone (157) (see Polymers containing sulfur, polysulfones). Poly(ether sulfone)s prepared from sodium 4-fluorobenzenethiolate, α,ω-diiodoperfluoroalkanes, and bisphenol A exhibit good permeability and selectivity for O_2–N_2 gas separations (158, 159). Fluorine-free membranes based on 2,6-difluorobenzonitrile and bisphenol A can also be used to separate gas mixtures (160, 161).

Less activated substrates such as fluorohalobenzenes also undergo nucleophilic displacement and thereby permit entry to other useful compounds. Bromine is preferentially displaced in *p*-bromofluorobenzene

[460-00-4] by hydroxyl ion under the following conditions: calcium hydroxide, water, cuprous oxide catalyst, 250°C, 3.46 MPa (500 psi), to give *p*-fluorophenol [371-41-5] in 79% yield (162, 163). This product is a key precursor to sorbinil, an enzyme inhibitor (aldose reductase).

2.3.3. Fluoroaryl Organometallics

Fluorobenzene does not form a Grignard reagent with magnesium (164). 4-Bromofluorobenzene [460-00-4] can be selectively converted to 4-fluorophenylmagnesium bromide [352-13-6] for subsequent incorporation into the silicon-containing fungicide, flusilazole [85509-19-9] (165).



This represents the first large-scale application of a fluoroaryl organometallic. Other silicon-containing aryl fluorides such as pentafluorophenyldimethyl silanes, $C_6F_5Si(CH_3)_2X$ (X = Cl; NH_2; $N(C_2H_5)_2$), are offered commercially as Flophemsyl reagents for derivatization of sterols in chromatographic analysis (166).

Phenyllithium cannot be formed from fluorobenzene. Instead, the electronegativity of fluorine makes the ortho hydrogen sufficiently acidic to permit reaction with *n*-butyllithium in tetrahydrofuran at $-50°C$ to give 2-fluorophenyllithium [348-53-8]. An isomer, 4-fluorophenyllithium [1493-23-8], was reported to be explosive in the solid state (167).

The chelate, cobalt bis(3-fluorosalicylaldehyde)ethyleneimine [6220-65-5] (fluomine) had been under active evaluation for an oxygen-regenerative system in aircraft (168). Boron-containing fluoroaromatics are commercially offered as laboratory reagents: tetrakis(4-fluorophenyl)boron sodium·$2H_2O$, a titration agent for nonionic surfactants (169); and 4-fluorobenzeneboronic acid [1765-93-1], a glc reagent for derivatization of diols.

2.3.4. Biotransformation Reactions

Enzymatic oxygenation of aryl fluorides without ring opening provides a new production tool to fluoroaromatic fine chemicals. Microbial oxidation of fluorobenzene forms 3-fluoro-*cis*-1,2-dihydrocatechol, followed by chemical rearomatization to give 3-fluorocatechol [363-52-0] (170–172). This technique represents a significant improvement over the standard four-step chemical route based on 3-fluoroanisole [456-49-5]. Dehydration (acid pH) of the fluorodihydrocatechol also provides a new route to 2-fluorophenol [367-12-4]. Biological oxidation of fluoroaromatics has been demonstrated at the tonnage scale in up to 20-m^3 reactors (171).

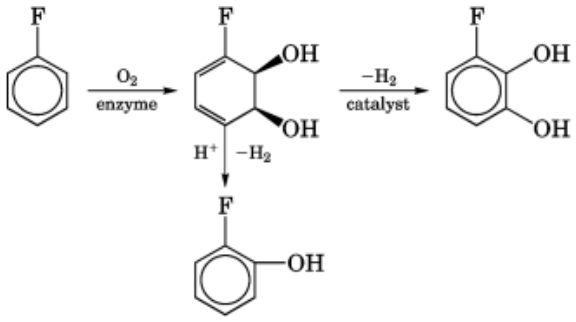
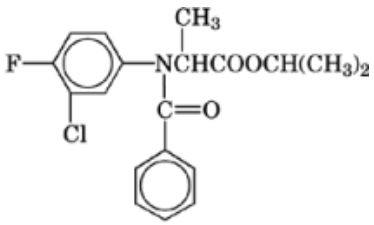
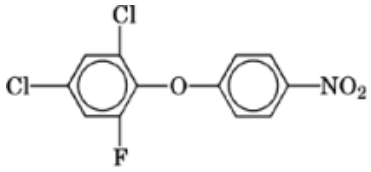
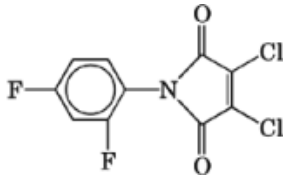
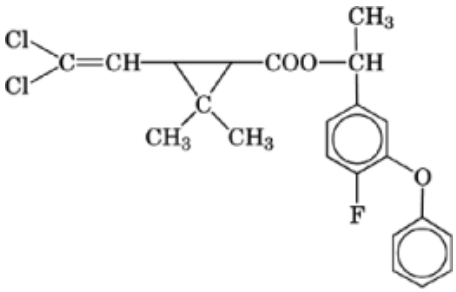
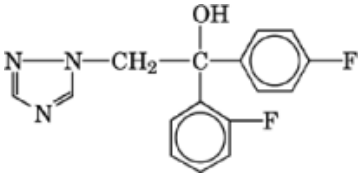


Table 3. Monofluoroaromatic Crop Protection Chemicals

Common name	CAS Registry Number	Structure	Application
flamprop-isopropyl	[52756-22-6]		post-emergent herbicide
fluoronitrofen	[13738-63-1]		post-emergent herbicide
fluoroimide	[41205-21-4]		fungicide
cyfluthrin	[68359-37-5]		insecticide
flutriafol	[76674-21-0]		fungicide

2.4. Manufacture

Fluorobenzene is produced by diazotization of aniline in anhydrous hydrogen fluoride at 0°C, followed by *in situ* decomposition of benzene-diazonium fluoride at 20°C (21). According to German experience during World War II, the yield for 750-kg batches was 75–77%. Aryldiazonium fluoride–hydrogen fluoride solutions can also be decomposed by continuous feed through a heated reaction zone (173, 174) or under super atmospheric pressure conditions (175).

The spent hydrogen fluoride layer, which contains water and sodium bifluoride, from this process is treated with sulfur trioxide or 65% oleum, and hydrogen fluoride is distilled for recycle to the next batch (176, 177)

Nitrosyl chloride (178), nitrosyl chloride–hydrogen fluoride (NOF·3HF, NOF·6HF) (179), nitrous acid–hydrogen fluoride solutions (180, 181), or nitrogen trioxide (prepared *in situ* from nitric oxide and oxygen) (27) can be used in place of sodium nitrite in the diazotization step.

Firms producing fluorobenzene and other ring-fluorinated aromatics by the diazotization of anilines in hydrogen fluoride include Rhône-Poulenc, ICI, Du Pont, Mallinckrodt, MitEni, and Riedel de Haën/Hoechst (182). With announcements of plant expansions and entry of new manufacturers, surplus capacity in basic fluoroaromatics exists. Prices (1991) are quoted at $15–18/kg delivered in the United States for basic intermediates such as fluorobenzene and the fluorotoluenes (182). Emphasis has now been placed on higher value downstream derivatives development programs.

Table 4. Monofluorinated Aromatic Drugs

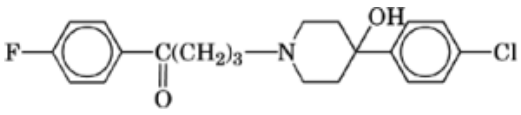
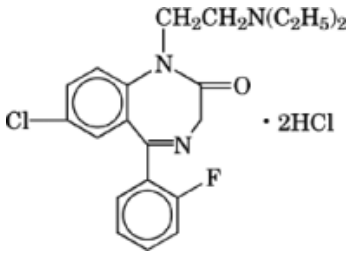
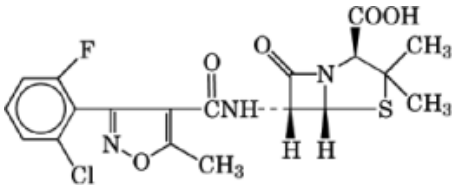
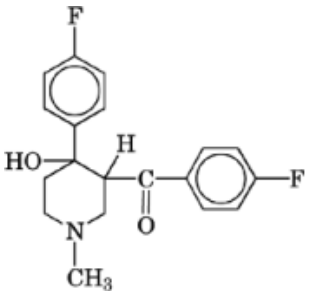
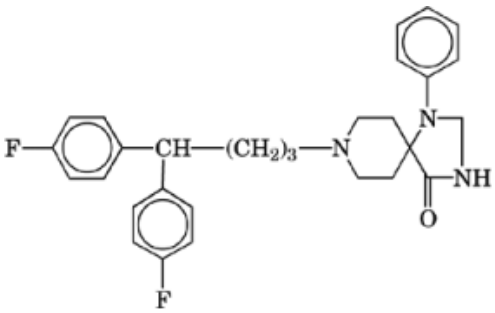
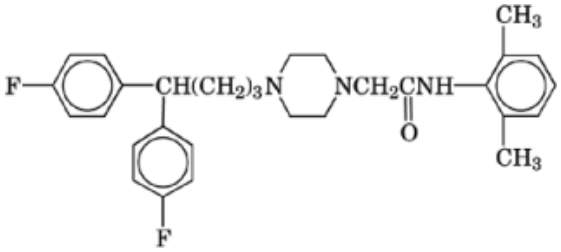
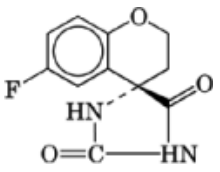
Common name	CAS Registry Number	Structure	Application
haloperidol	[52-86-8]		tranquilizer
flurazepam hydro-chloride	[1172-39-5]		hypnotic, sedative
floxacillin	[5250-39-5]		antibacterial

Table 4. ***Continued***

Common name	CAS Registry Number	Structure	Application
flazalone	[21221-18-1]		anti-inflammatory
fluspirilene	[1841-19-6]		tranquilizer
lidoflazine	[3416-26-0]		vasodilator (coronary)
sorbinil	[68367-52-2]		enzyme inhibitor (aldose reductase)

2.5. Applications

2.5.1. Crop Protection Chemicals

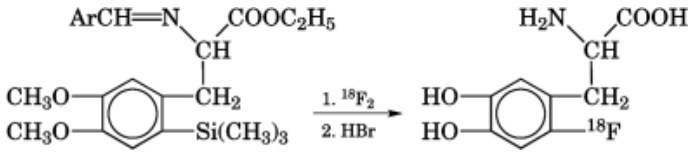
The fluorinated analogue of DDT (GIX, DFDT), 1,1-bis(4-fluorophenyl)-2,2,2-trichloroethane [475-26-3], was produced from chloral and fluorobenzene as an insecticide in Germany during World War II. Other agricultural applications did not subsequently materialize since lower manufacturing costs of chlorinated aromatic crop-protection chemicals represented an advantage over ring-fluorinated analogues. However, chloroaromatics pose ecological problems such as pesticide persistency, toxicity, etc. Because fluoroaromatics offer agronomic advantages, eg, dosage, selectivity, and crop safety, significant commercialization of these compounds as crop protection chemicals (herbicides, fungicides, and insecticides) has occurred. Table 3 lists representative examples.

2.5.2. Drugs

Ring-fluorinated aromatics have found broad pharmaceutical applications, eg, in tranquilizers, hypnotics, sedatives, antibacterial agents (qv), etc. Representative monofluorinated drugs are listed in Table 4. Arprinocid [5579-18-15] is a fluoroaromatic-based veterinary drug that has found wide acceptance as a coccidiostat for chicken feed.

2.5.3. Other Medical Applications

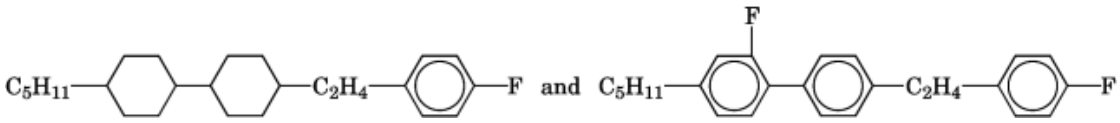
Positron emission tomography, a noninvasive technique for monitoring biochemical functions in humans, represents a significant advance in medical diagnosis. Synthetic methods have been developed for incorporation of the ^{18}F isotope ($t_{1/2}$, 109.27 ± 0.06 min) into numerous biologically active radiopharmaceuticals (1). One example is the stereospecific and regiospecific synthesis of 6-[^{18}F]fluoroDOPA (6-fluoro-3,4-dihydroxyphenylalanine) by fluorodemetallation of a trimethylsilyl precursor using $^{18}F_2$ for Parkinson's disease research.



Labeling aromatics with fluorine using ^{19}F-nmr as a probe for product identification has been a useful analytical tool (183) which has been extended to medical diagnosis. Magnetic resonance imaging (mri) is a noninvasive technique complementary to x-ray contrast agents, ultrasound devices, and computerized tomography, without the need of radioisotopes (184). For example, the mri technique has been applied to the interaction of fluoroquine, a fluorine analogue of the antimalarial drug, chloroquine, with DNA and *t*-RNA (185).

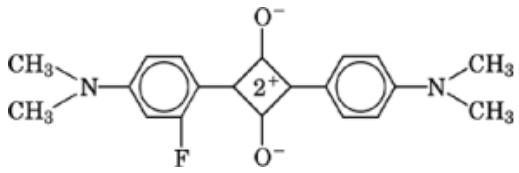
2.6. Liquid Crystals

Based on worldwide patent activity, numerous compounds containing fluoroaromatic moieties have been synthesized for incorporation into liquid crystals. For example, fluoroaromatics are incorporated in ZLI-4792 and ZLI-4801-000/-100 for active matrix displays (AMD) containing super fluorinated materials (SFM) (186, 187). Representative structures are as follows.



2.6.1. Photoconductive Imaging

Considerable attention has been placed on the xerographic properties of fluorosquaraines based on *N,N*-dimethyl-3-fluoroaniline and other 3-fluoroaniline derivatives for imaging applications (188–191). A typical structure of a fluorosquaraine is as follows:



2.6.2. Dyes

In contrast to benzotrifluorides and fluoropyrimidines, limited commercialization has developed for dyes containing a fluoroaromatic group. Fluorophenylhydrazines have been converted to (fluorophenyl)pyrazolones, which are disperse dyes for cellulose acetate and nylon (192).

2.7. Difluorobenzenes

Interest in the commercialization of difluoroaromatics in crop protection chemicals and drugs (Table 5) continues to be strong. Numerous liquid crystals containing the 1,2-difluorobenzene moiety have been synthesized. Table 6 lists physical properties of commercially significant intermediates such as *o-, m-,* and *p*-difluorobenzene, 2,4-difluoroaniline and 2,6-difluorobenzonitrile. The LD_{50} values for the three isomeric difluorobenzenes are identical: 55 g/m^3 for 2 h (inhalation, mouse) (127).

Table 5. Difluoroaromatic Applications

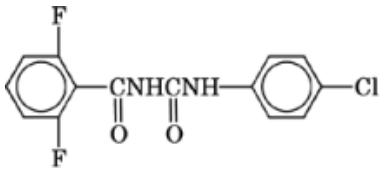
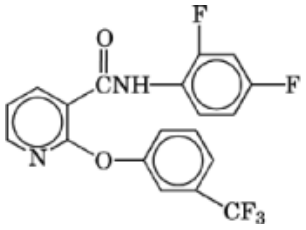
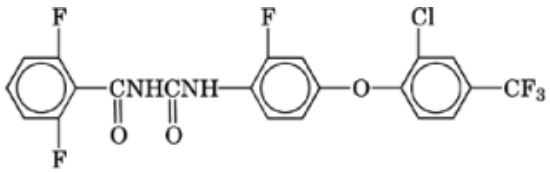
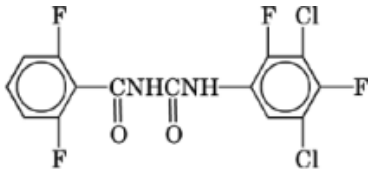
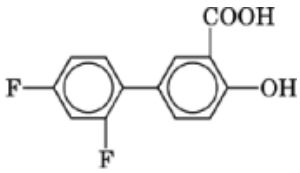
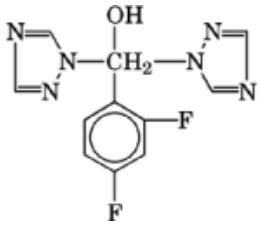
Common name	CAS Registry Number	Structure
	Crop protection chemicals[a]	
diflubenzuron	[35367-38-5]	
diflufenican[b]	[83164-33-4]	

Table 5. ***Continued***

Common name	CAS Registry Number	Structure
flufenoxuron	[101463-69-8]	
teflubenzuron	[83121-18-0]	
		Drugs
diflunisal[c]	[22494-42-4]	
fluconazole[d]	[86386-73-4]	

[a] Insecticide unless otherwise noted.
[b] Herbicide.
[c] Analgesic; antiinflammatory.
[d] Antifungal.

2.8. 1,2-Difluorobenzene

Tetrazotization-fluorination of *o*-phenylenediamine [95-54-5] in hydrogen fluoride or by the Balz-Schiemann reaction is not a practical route to 1,2-difluorobenzene but this product can be prepared from 2-fluoroaniline [348-54-9] by the Balz-Schiemann reaction (193); heating the diazonium fluoroborate in organic solvents increases the yield to 78% (194). Electrophilic substitution reactions are site-specific: nitration gives

Table 6. Properties of Fluorinated Aromatic Compounds[a]

Component	CAS Registry Number	Mol wt	Mp, °C	Bp, °C[b]	Refractive index, n_D^t	Specific gravity, d_4^t	Surface tension, 20°C mN/m (=dyn/cm)	Flash point,[c] °C
				Difluorobenzenes				
$C_6H_4F_2$								
1,2-difluorobenzene	[367-11-3]	114.09	−34	91–92	1.4452^{20}	1.1496^{25}		7.2[d]
1,3-difluorobenzene	[372-18-9]	114.09	−59.3	82–83	1.4410^{20}	1.1572^{20}	25.93	−11.1[d]
1,4-difluorobenzene	[540-36-3]	114.09	−13	88–89	1.4421^{20}	1.1716^{20}	27.05	−11.7[d]
				Trifluorobenzenes				
$C_6H_3F_3$								
1,2,3-trifluorobenzene	[1489-53-8]	132.08		94–95	1.4230^{20}	1.280^{20}		−3
1,2,4-trifluorobenzene	[367-23-7]	132.08		88	1.4230^{20}	1.264^{20}	26.2	−5[d]
1,3,5-trifluorobenzene	[372-38-3]	132.08	−5.5	75.5	1.4140^{20}	1.277^{20}	27.16	−7
				Tetrafluorobenzenes				
$C_6H_2F_4$								
1,2,3,4-tetrafluorobenzene	[551-62-2]	150.08	−42	95	1.4069^{20}	1.422^{25}		20
1,2,3,5-tetrafluorobenzene	[2367-82-0]	150.08	−48	83	1.4011^{25}	1.393^{20}	23.99	4
1,2,4,5-tetrafluorobenzene	[327-54-8]	150.08	4	90	1.4045^{20}	1.424^{25}	24.9	16
				Pentafluorobenzene				
C_6HF_5	[363-72-4]	168.07	−48	85	1.3881^{25}	1.531^{20}		13
2-fluorotoluene[e]	[95-52-3]	110.13		113–114	1.4704^{25}	1.001^{20}		12
3-fluorotoluene	[352-70-5]	110.13		115	1.4691^{20}	0.991^{20}		9
4-fluorotoluene	[352-32-9]	110.13		116	1.4690^{20}	1.000^{20}		17
2-chloro-6-fluorotoluene	[443-83-4]	144.58		155	1.5026^{20}	1.129^{20}		48
				Fluoroanilines				
$C_6H_4F(NH_2)$								
2-fluoroaniline[f]	[348-54-9]	111.12	−29	175	1.5406^{25}	1.152^{25}		60
3-fluoroaniline[g,h]	[372-19-0]	111.12		186	1.5445^{25}	1.152^{25}		77
4-fluoroaniline[e,f,i]	[371-40-4]	111.12	−1.9	187	1.5375^{25}	1.158^{25}		73
$C_6H_3F_2(NH_2)$ 2,4-difluoroaniline	[367-25-9]	129.11	−7.5	169.5	1.5043^{25}	1.268^{20}		62
$C_6H_3(Cl)(F)(NH_2)$ 3-chloro-4-fluoroaniline	[367-21-5]	145.57	44–47	227–228		1.42^{20} (solid) 1.3^{60} (liquid)		110
				Fluorobenzonitriles				
2,6-difluorobenzonitrile	[1897-52-5]	139.11	30–32	99[j]	1.4875^{25}	1.236^{40}		80

[a] Colorless unless otherwise noted.
[b] At 101.1 kPa = 1 atm unless otherwise noted.
[c] Closed cup (ASTM Procedure D3278) unless otherwise noted.
[d] Open cup.
[e] LD_{50} = 100 mg/kg (oral, wild bird) (127).
[f] Pale yellow.
[g] Amber.
[h] LD_{50} = 56 mg/kg (oral, wild bird) (127).
[i] LD_{50} = 50 mg/kg (oral, rat) (127).
[j] At 2.67 kPa = 20 mm Hg.

3,4-difluoronitrobenzene [369-34-6], and bromination forms 3,4-difluorobromobenzene [348-61-8], a precursor to dicyclohexylethylene liquid crystals (195). Vicinal metallation (*n*-butyllithium, −78°C) of 1,2-difluorobenzene is also employed to prepare *trans*-4-alkyl cyclohexyl-substituted 2,3-difluorobiphenyls for liquid crystal applications (196).

2.9. 1,3-Difluorobenzene

This isomer has been prepared in 78% yield by tetrazotization-fluorination of *m*-phenylenediamine [108-45-2] in pyridine–hydrogen-fluoride at 100°C (23, 197). Balz-Schiemann yields for the corresponding reaction vary from 31 to 49% (198, 199). Diazotization of *m*-fluoroaniline [372-19-0] in the presence of ammonium bifluoride, tertiary amines, or dimethyl sulfoxide gave 46–73% yields of 1,3-difluorobenzene (25, 26). The latter can also be made by reductive-dediazoniation of 2,4-difluoroaniline [367-25-9] in 77% yield from sodium nitrite, hydrochloric acid, and hypophosphorus acid (200). A 95% yield was realized by treatment of 2,4-difluorobenzenediazonium fluoroborate with copper powder in the presence of 18-crown-6 ether in dichloromethane (201).

Nitration of 1,3-difluorobenzene at 0°C forms 2,4-difluoronitrobenzene [446-35-5] in 92% yield. The latter can also be prepared from 2,4-dichloronitrobenzene and potassium fluoride in polar solvents (46, 202); phase-transfer catalysts, eg, quaternary ammonium salts, serve to both lower reaction temperature and enhance fluorination rates (203). Reduction gives 2,4-difluoroaniline, a precursor to the analgesic/antiinflammatory diflunisal, and the herbicide diflufenican.

2.10. 1,4-Difluorobenzene

This compound has been prepared in 65% yield by tetrazotization-fluorination of *p*-phenylenediamine [106-50-3] in pyridine–hydrogen fluoride at 120°C (23, 197); 27–40% yields are obtained by the Balz-Schiemann reaction with *p*-phenylenediamine or *p*-fluoroaniline [371-40-4] (198).

2.11. Trifluorobenzenes

Table 6 lists physical properties of representative trifluorobenzenes.

2.12. 1,2,3-Trifluorobenzene

This compound is formed in low yield (13–24%) from 1,2,3-trichlorobenzene or 2,3-difluorochlorobenzene and KF/CsF in dimethyl sulfone (204). Likewise, low yields are realized when the Balz-Schiemann reaction is applied to 2,3-difluoroaniline or 2,6-difluoroaniline (205). Pyrolysis (520°C, iron gauze) of 1*H,* 2*H,* 3*H*-pentafluorocyclohexa-1,3-diene forms 1,2,3-trifluorobenzene (206). Derivatives such as 2,3,4-trifluoronitrobenzene [393-79-3] and 2,3,4-trifluoroaniline [3862-73-5] have been used to prepare fluoroquinolone antibacterials such as ofloxacin (207) and lomefloxacin (208), respectively.

2.13. 1,2,4-Trifluorobenzene

This isomer can be prepared in good yield from 2,4-difluoroaniline by the standard Balz-Schiemann route (209) or modifications using nitrite esters–boron trifluoride (210). Its ionization potential is 9.37 V. Electrophilic substitution reactions of 1,2,4-trifluorobenzene provide useful routes to 2,4,5-trifluorobenzoic acid [446-17-3], a key precursor to fluoroquinolone antibacterials: bromination forms 1-bromo-2,4,5-trifluorobenzene [327-52-6] (211), followed by exchange cyanation–hydrolysis (212); acetylation gives 2,4,5-trifluoroacetophenone [129322-83-4], followed by oxidation with commercial bleach (213). New routes to 2,4,5-trifluorobenzoic acid are also based on exchange-fluorination of chloroaromatic feedstocks such as 3,4,6-trichlorophthalic acid (62) and tetrachloroisophthalonitrile (214). Other 1,2,4-trifluorobenzene derivatives such as 3-chloro-2,4,5-trifluorobenzoic acid have also been converted to fluoroquinolone antibacterials (215).

2.14. 1,3,5-Trifluorobenzene

This isomer, *s*-trifluorobenzene, has been prepared in 63% yield by the Balz-Schiemann reaction with 3,5-difluoroaniline [372-39-4] (216). By modification of exchange fluorination conditions, tetrachloroisophthalonitrile [1897-45-6] was converted to 1,3,5-trifluorobenzene by a four-step process (217).

2.15. Tetrafluorobenzenes

Interest in tetrafluoroaromatics includes crop protection and as intermediates to fluoroquinolone antibacterials. Physical properties of tetrafluorobenzenes are listed in Table 6. A useful compilation of recipes for 35 tetrafluorinated aromatics has been published (199).

2.16. 1,2,3,4-Tetrafluorobenzene

This compound has been prepared by fluorination of benzene with cobalt trifluoride and subsequent combination of the dehydrofluorination and defluorination steps. Its ionization potential is 9.01 V. Nitration gives 2,3,4,5-tetrafluoronitrobenzene [5580-79-0] in 75% yield, an intermediate to fluoroquinolone antibacterials (218).

Halex technology has also been employed to prepare 1,2,3,4-tetrafluorobenzene derivatives, eg, tetrachlorophthalic anhydride [117-08-8] was converted to 2,3,4,5-tetrafluorobenzoic acid [1201-31-6] for use in fluoroquinolone antibacterials (219, 220).

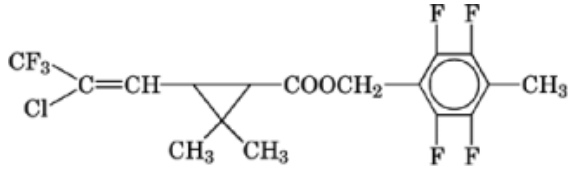
2.17. 1,2,3,5-Tetrafluorobenzene

This isomer has been prepared from 2,3,5-trifluoroaniline [363-80-4] in 43% yield by the Balz-Schiemann reaction.

2.18. 1,2,4,5-Tetrafluorobenzene

This compound has been prepared from 2,4,5-trifluoroaniline [57491-45-9] by the Balz-Schiemann reaction in 38–46% yield or from pentafluorophenylhydrazine [828-39-9] with aqueous sodium hydroxide in 90–95% yield (221). Its ionization potential is 9.39 V.

Derivatives of 1,2,4,5-tetrafluorobenzene such as 2,3,5,6-tetrafluorobenzoic acid have been converted into fluoroquinolone antibacterials (222–224). The synthetic pyrethroid, tefluthrin [795-38-2], is prepared from 2,3,5,6-tetrafluoro-4-methylbenzyl alcohol.



Isomeric dichlorotetrafluorobenzenes have been studied for Rankine-cycle external combustion engines (225).

2.19. Pentafluorobenzene and Pentafluorophenyl Compounds

2.20. Pentafluorobenzene

Pentafluorobenzene has been prepared by several routes: multistage saturation–rearomatization process based on fluorination of benzene with cobalt trifluoride; reductive dechlorination of chloropentafluorobenzene with 10% palladium-on-carbon in 82% yield (226, 227); and oxidation of pentafluorophenylhydrazine in aqueous copper sulfate at 80°C in 77% yield (228). Its ionization potential is 9.37 V. One measure of toxicity is LD_{50} = 710 mg/kg (oral, mouse) (127).

Nucleophiles react with pentafluorobenzene to give para-substituted (relative to the hydrogen atom) tetrafluorophenyl products, p-XC_6F_4H (X = H, NH_2, $NHNH_2$, SH, OCH_3, SC_6H_5, OH). Nitration of pentafluorobenzene with concentrated nitric acid and boron trifluoride in sulfolane gave pentafluoronitrobenzene [880-78-4] in 82% yield (229).

2.21. Pentafluoroaniline

Pentafluoroaniline [771-60-8] has been prepared from amination of hexafluorobenzene with sodium amide in liquid ammonia or with ammonium hydroxide in ethanol (or water) at 167–180°C for 12–18 h. It is weakly basic (pK_a = 0.28) and dissolves only in concentrated acids. Liquid crystals have been prepared from Schiff bases derived from pentafluoroaniline (230).

2.22. Pentafluorophenol

This compound has been prepared from the reaction of hexafluorobenzene with potassium hydroxide in t-butyl alcohol. Pentafluorophenyl esters prepared from pentafluorophenol [771-61-9] illustrate the key features of a rapid stepwise peptide synthesis technique (231). Commercial high performance elastomers based on copolymerization of tetrafluoroethylene, perfluoro(methyl vinyl ether), and a third monomer incorporating a pentafluorophenoxy group as a cure site, give vulcanizates with good chemical and fluid resistance and high temperature oxidative resistance (232, 233).

2.23. Pentafluorotoluene

Pentafluorotoluene [771-56-2] has been prepared from the reaction of methyllithium with hexafluorobenzene or from pentafluorophenyl-magnesium bromide with dimethyl sulfate. Derivatives such as 2,3,4,5,6-pentafluorobenzyl bromide [1765-40-8] are used to derivatize organic acids as esters for determination by electron-capture gas chromatography (234). The synthetic pyrethroid, fenfluthrin [75867-00-4], is an insecticide containing a pentafluorobenzyl group.

2.24. Bromopentafluorobenzene

Aluminum bromide-catalyzed bromination of pentafluorobenzene in 20% oleum gives bromopentafluorobenzene [1765-40-8]. It is readily converted to pentafluorophenylmagnesium bromide [879-05-0]; the latter undergoes conventional Grignard reactions (qv). Pentafluorophenyllithium [1076-44-4] can be synthesized from bromopentafluorobenzene and n-butyllithium or lithium amalgam in ether at 0°C. The preferred route is metallation of pentafluorobenzene with n-butyllithium at -65°C (235). A serious explosion has been reported during hydrolysis (D_2O) of pentafluorophenyllithium (236).

Pentafluorophenylmagnesium bromide or lithium can be converted to other pentafluorophenyl organometallics by reaction with the corresponding metal chloride (237).

Bis(pentafluorophenyl)phenylphosphine [5074-71-5] (Ultramark 443), $(C_6F_5)_2C_6H_5P$, is offered commercially as a marker for mass spectral standardization (238).

2.25. Pentafluorobenzoic Acid

Standard routes to pentafluorobenzoic acid [602-94-8] include chloropentafluorobenzene (*n*-butyllithium or magnesium, carbonation, hydrolysis); pentafluorobenzene (phosgene, hydrolysis); octafluorotoluene (hydrolysis). Of potential economic significance is a new route based on benzonitrile: chlorination to pentachlorobenzonitrile, exchange fluorination, and hydrolysis (239). Pentafluorobenzoyl chloride [2251-50-8] has been used to derivatize anticonvulsants such as ethosuximide, carbamazepine, and primidone in electron-capture gas chromatography (240, 241).

2.26. Pentafluorobenzaldehyde

Pentafluorobenzaldehyde [653-37-2] can be prepared by reaction of *N*-methylformanilide with pentafluorophenylmagnesium bromide or pentafluorophenyllithium. One process is based on the catalytic hydrogenation of pentafluorobenzonitrile (239). Pentafluorobenzaldehyde is used as a reagent for gas chromatographic assay of biological amines such as catecholamines by conversion to the pentafluorobenzylimine–trimethylsilyl derivatives (242). Catalytic hydrogenation gives pentafluorobenzyl alcohol [440-60-8]. Derivatives of the latter are employed in gas chromatography (electron capture): *O*-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine hydrochloride [57981-02-9] (Florox reagent) $C_6F_5CH_2ONH_2{\cdot}HCl$, for assay of ketosteroids (243, 244); 2,3,4,5,6-pentafluorobenzyl chloroformate [53526-74-2], for assay of physiologically active tertiary amines (245).

Numerous examples for the incorporation of the pentafluorophenyl group in chromatographic derivatization of biologically active compounds have been compiled in a monograph (246). A review on the effects of the pentafluorophenyl group on the reactivity of organic compounds has been published (247).

2.27. Hexafluorobenzene

The development of commercial routes to hexafluorobenzene [392-56-3] included an intensive study of its derivatives. Particularly noteworthy was the development of high temperature lubricants, heat-transfer fluids, and radiation-resistant polymers (248).

2.28. Hexafluorobenzene

Hexafluorobenzene [392-56-3] C_6F_6, is a colorless liquid with a sweet odor. Hexafluorobenzene (perfluorobenzene) has a good thermal stability; slight decomposition occurs at 500°C in Nimonic 75 (alloy containing 85% nickel and 20% chromium) after three weeks. Toxicity: inhalation (mouse), LD_{50}-95 g/m^3 (2 h) (127). Physical properties of hexafluorobenzene are given in Table 7.

2.29. Manufacture

One commercial process features a three-stage saturation–rearomatization technique using benzene and fluorine gas as raw materials (73). Principal problems with this method are the complex nature of the process, its dependence on fluorine gas which is costly to produce, and the poor overall utilization of fluorine, because nearly one-half of the input fluorine is removed during the process.

An alternative hexafluorobenzene process features exchange fluorination (KF) of hexachlorobenzene in the presence of polar solvents (226, 249) or under solvent-free conditions (450–540°C, autoclave) (250). Intermediates such as chloropentafluorobenzene can be further fluorinated to hexafluorobenzene (42–51% yield) by cesium fluoride in sulfolane (226, 249).

Table 7. Physical Properties of Hexafluorobenzene

Property	Value
mol wt	186.06
melting point, °C	5.10
boiling point, °C	80.261
density, 25°C, g/mL	1.60682
refractive index, n_D^{25}	1.3761
latent heat of fusion, kJ/mol[a]	11.59
latent heat of vaporization	
at 25°C, kJ/mol[a]	35.69 ± 0.084
at bp, kJ/mol[a]	32.69
specific heat, 23°C, kJ/mol·°C)[a]	0.221
critical temperature, °C	243.57 ± 0.03
critical pressure, MPa[b]	3.304 ± 0.005
coefficient of cubical expansion at 25°C	0.001412
heat of combustion, kJ/mol[a]	−2444.0 ± 1.2
heat of formation at 25°C, kJ/mol[a]	
liquid	−958.30
gas	−922.15
vapor pressure in °C and kPa[c]	Antoine equation[d]

[a] To convert J to cal, divide by 4.184.
[b] To convert MPa to atm, divide by 0.101.
[c] To convert kPa to mm Hg, multiply by 7.5; $\log kPa = \log mm\ Hg - 0.875$.

[d] $\mathrm{Log}_{10}P = 6.1422 - \dfrac{1219.410}{(t + 214.525)}$.

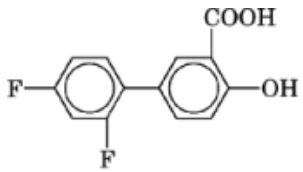
Pyrolytic routes to hexafluorobenzene have also attracted attention but have not been commercialized. Pyrolysis of tribromofluoromethane [353-54-8], CBr_3F, at 630–640°C in a platinum tube gives hexafluorobenzene in 55% yield (251–253). The principal disadvantage of this process is the low weight yield of product; 90% of the costly CBr_3F that is charged is lost as bromine. Of economic potential is the related copyrolysis of dichlorofluoromethane [754-34-0] and chlorofluoromethane [593-70-4] (254, 255).

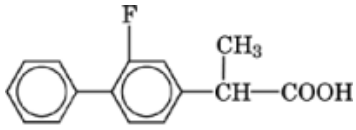
2.30. Reactions

Hexafluorobenzene is susceptible to attack by nucleophilic agents to give pentafluorophenyl compounds of the general formula C_6F_5X, where X is OCH_3, NH_2, OH, SH, $NHNH_2$, $NHCH_3$, $N(CH_3)_2$, H, C_6H_5, CH_3, $CH_3CH{=}CH$, n-C_4H_9, C_6H_5S, etc (256).

2.31. Fluorobiphenyls

Fluorobiphenyls are incorporated into the analgesic and antiinflammatory drugs diflunisal [22494-42-4] and flurbiprofen [5104-49-4]. The first is a difluoro compound and the other monofluoro.





Fluorinated biphenyls have been incorporated into numerous liquid crystal structures as attested by patents and publications from the following organizations: E. Merck GmbH (257, 258); Sharp (258); Hoffmann-LaRoche (259); Kanto Chemical (260); U.K. Defence Secretariat (261); Dainippon (262); Chisso (263); Sanyo Chemical (264); and the University of Hull (265). Seiko Epson has also patented fluorinated terphenyls for liquid crystal applications (266).

Fluorinated biphenyls can be synthesized by diazotization–fluorination, Gomberg-Bachmann arylation, or Ullmann coupling reactions. Mono- and difluorophenyls can be prepared by the Balz-Schiemann reaction (or modification in HF), eg, 4,4′-difluorobiphenyl was formed in 80% yield from 4,4′-diaminobiphenyl by the Balz-Schiemann reaction (267). 2,4-Difluorobiphenyl [2285-28-1], a key precursor to diflunisal, is formed by successive diazotization of 2,4-difluoroaniline and coupling with benzene (268). Similar diazotization-coupling of 4-bromo-2-fluoroaniline [367-24-8] with benzene gives 4-bromo-2-fluorobiphenyl [41604-19-7], a key intermediate to flurbiprofen (269).

Decafluorobiphenyl [434-90-2], $C_6F_5C_6F_5$ (mol wt, 334.1; mp, 68°C; bp, 206°C), can be prepared by Ullmann coupling of bromo- [344-04-7], chloro- [344-07-0], or iodopentafluorobenzene [827-15-6] with copper. This product shows good thermal stability; decafluorobiphenyl was recovered unchanged after 1 h below 575°C (270). Decafluorobiphenyl-based derivatives exhibit greater oxidative stability than similar hydrocarbon compounds (271). Thermally stable poly(fluorinated aryl ether) oligomers prepared from decafluorobiphenyl and bisphenols show low dielectric constant and moisture absorption which are attractive for electronic applications (272).

3. Fluoronaphthalenes and Other Fused-Ring Fluoroaromatics

Few applications for fluoronaphthalenes and related polycyclic structures have materialized. The fused-ring bicyclic, sulindac [38194-50-2], a monofluorinated indene-3-acetic acid, is used as an antiinflammatory agent.

1-Fluoronaphthalene [321-38-0] is prepared from 1-naphthylamine by the Balz-Schiemann reaction in 52% yield or by diazotization in anhydrous hydrogen fluoride in 82% yield. Electrophilic substitution occurs at the 4-position, eg, nitration with fuming nitric acid in acetic acid gave 88% yield of 1-fluoro-4-nitro-naphthalene [341-92-4].

2-Fluoronaphthalene [323-09-1] is prepared in 54–67% yield from 2-naphthylamine by the Balz-Schiemann reaction or in 51% yield by pyrolysis of indene and chlorofluoromethane at 600°C (77).

1,4-Difluoronaphthalene [315-52-6] is prepared from 4-fluoro-1-naphthylamine by the Balz-Schiemann reaction. 1,4-Difluoronaphthalene is used in chemical carcinogenesis studies as a synthon for highly condensed difluoro–polycyclic aromatic hydrocarbons (273).

Octafluoronaphthalene [313-72-4] is prepared in 53% yield by defluorination of perfluorodecahydronaphthalene [306-94-5] over iron or nickel at 500°C. Exchange fluorination of octachloronaphthalene with KF in sulfolane (235°C) gave 60% yield of octafluoronaphthalene. This product exhibits good stability to ionizing radiation (274).

Fused-ring polycyclic fluoroaromatics can be made from the corresponding amino fused-ring polycyclic or from preformed fluoroaromatics, eg, 4-fluorophenyl-acetonitrile [459-22-3] (275). Direct fluorination techniques have been successfully applied to polycyclic ring systems such as naphthalene, anthracene, benzanthracenes, phenanthrene, pyrene, fluorene, and quinolines with a variety of fluorinating agents: xenon fluorides (10), acetyl hypofluorite (276), cesium fluoroxysulfate (277), and electrochemical fluorination (278, 279).

4. Side-Chain Fluorinated Aromatics

Trifluoromethyl aromatics are used widely in the production of drugs, crop-protection chemicals, germicides, dyes, etc.

4.1. General Properties

The trifluoromethyl group is stable under different reaction conditions, eg, the multistep classical transformation of benzotrifluoride to trifluoroacetic acid features successive nitration, reduction, and oxidation.

4.1.1. Thermal Stability

Benzotrifluoride is stable at 350°C in the presence of iron or copper. Working fluids for external combustion engines (Rankine cycle) must exhibit thermal stability with engine materials at high temperatures. Some of the promising working fluids include 1,3-bis(trifluoromethyl)benzene [402-31-3] (280) or a mixture of perfluorotoluene [434-64-0], $CF_3C_6F_5$, and hexafluorobenzene [392-56-3] (281). The stability of the isomeric CF_3-substituted anilines has been established by differential thermal analysis (dta) (282): *m*-$CF_3C_6H_4NH_2$ [98-15-7], 223°C > *o*-$CF_3C_6H_4NH_2$ [88-17-5], 187°C > *p*-$CF_3C_6H_4NH_2$ [455-14-1], 155°C.

4.1.2. Hydrolytic Stability

The trifluoromethyl group is sensitive to hydrolysis in acidic media. Benzotrifluoride is hydrolyzed to benzoic acid by heating with hydrobromic, hydrofluoric, or >80% sulfuric acid. Reaction conditions and structural features for this reaction have been summarized (283). Benzotrifluorides are generally stable to base. Benzotrifluoride was recovered unchanged after heating (120–130°C) with sodium hydroxide. Although *m*-hydroxybenzotrifluoride [98-17-9] is stable to refluxing 50% sodium hydroxide, cold dilute alkali polymerizes the para isomer [402-45-9] (284). Similar polymers are formed from 2,3,5,6-tetra-fluoro-4-trifluoromethylphenol [2787-79-3] (285). Photohydrolysis of hydroxy- and aminobenzotrifluorides in dilute acid and alkali, respectively, gives the corresponding hydroxy- and aminobenzoic acid in high yield (286). Benzotrifluoride is inert under these photohydrolytic conditions.

4.1.3. Oxidative Stability

Benzotrifluoride resists ring oxidation. In contrast, chromic acid readily oxidizes 3-aminobenzotrifluoride to trifluoroacetic acid in 95% yield (287).

4.1.4. Stability to Reducing Agents

The trifluoromethyl group is inert to numerous reducing agents. Catalytic hydrogenation (platinum black) of benzotrifluoride gives trifluoromethylcyclohexane [401-75-2] (288). Benzotrifluoride was not reduced by lithium aluminum hydride (289). However, *o*-trifluoromethylbenzoic acid [433-97-6] and *m*-trifluoromethylbenzoic acid [454-92-2] are catalytically reduced (Raney nickel or cobalt alloys) to *o*- and *m*-toluic acid, respectively (290).

4.1.5. Instability of Trifluoromethylphenyl Organometallics

Care must be exercised in handling trifluoromethylphenyl organometallics. *o*-Trifluoromethylphenyllithium [49571-35-5] has exploded during reflux in diethyl ether under nitrogen (291). Both *m*- [368-49-0] and *p*-trifluoromethylphenyllithium [2786-01-8] are explosive in the solid state (292). Explosions have been reported in the preparation of *o*- [395-47-1], *m*- [402-26-6], and *p*-trifluoromethylphenylmagnesium bromide [402-51-7] (292, 293). A violent explosion accompanied by loss of life and destruction of a chemical plant during preparation of *p*-trifluoromethylphenylmagnesium chloride [2923-41-3] has been reported (294). A compilation of reactive chemical hazards of trifluoromethylphenyl organometallics was published in 1990 (68).

4.2. Reactions

Benzotrifluoride undergoes electrophilic substitution reactions, eg, halogenation, nitration, typical of an aromatic containing a strong electron-withdrawing group. The trifluoromethyl group (sometimes referred to as a pseudohalogen) is meta directing.

4.2.1. Halogenation

Liquid-phase monochlorination of benzotrifluoride gives pronounced meta orientation (295); in contrast, vapor-phase halogenation favors para substitution (296). Sealed tube, photochemical, or dark chlorination (radical initiator) forms hexachloro(trifluoromethyl)cyclohexane; thermal dehydrochlorination (550°C) gives 2,4,6-trichlorobenzotrifluoride [567-59-9] (297). Liquid-phase bromination (Br_2) provides 3-bromobenzotrifluoride [401-78-5] in 60% yield. Catalyst performance decreases in the order $FeCl_3 > Fe > SbCl_5 > I_2$ (298). Silica gel (299) and calcium chloride (300) serve as hydrogen fluoride scavengers to suppress corrosion of glass reactors during halogenation. Bromination of benzotrifluoride can also be accomplished with bromine chloride in the presence of a halogen carrier, eg, antimony pentachloride; this technique permits complete utilization of bromine (301).

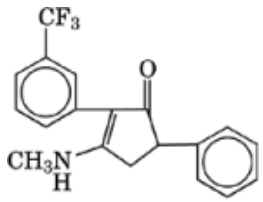
Hydrogen peroxide–hydrochloric acid reagent converts 2-aminobenzotrifluoride to 2-amino-5-chlorobenzotrifluoride [121-50-6], a dye intermediate (CI Azoic Diazo Component 17), without contamination by the 3-chloro isomer such as is observed with molecular chlorine (Cl_2) (302).

4.2.2. Nitration

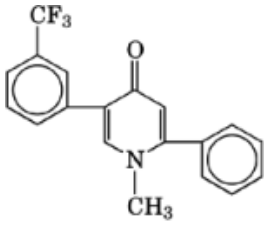
Nitration of benzotrifluorides is an important industrial reaction. Mononitration of benzotrifluoride gives pronounced meta-orientation: 91% meta [98-46-4]; 6% ortho [384-22-5]; and 3% para [402-54-0] (296). Further nitration to 3,5-dinitrobenzotrifluoride [401-99-0] can be affected under forcing conditions at 100°C.

4.2.3. Alkylation

Benzotrifluoride can also be alkylated, eg, chloromethyl methyl ether–chlorosulfonic acid forms 3-(trifluoromethyl)benzyl chloride [705-29-3] (303, 304), which can also be made from *m*-xylene by a chlorination–fluorination sequence (305). Exchange cyanation of this product in the presence of phase-transfer catalysts gives 3-(trifluoromethylphenyl)acetonitrile [2338-76-3] (304, 305), a key intermediate to the herbicides flurtamone [96525-23-4] (306) and fluridone [59756-60-4].



flurtamone



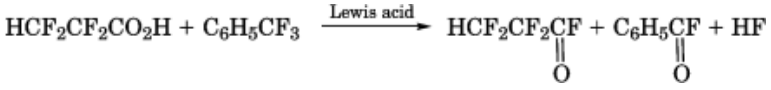
fluridone

4.2.4. Nucleophilic Displacement Reactions

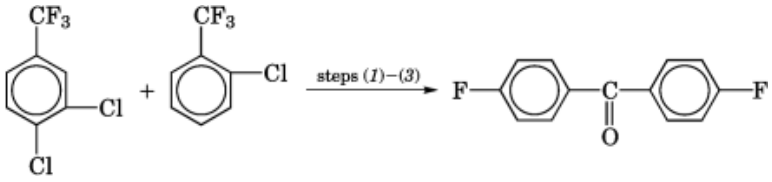
The strong electron-withdrawing effect of a trifluoromethyl group activates ortho and para halogen toward nucleophilic attack. Such chlorine lability is utilized in the manufacture of crop control chemicals containing trifluoromethyl and nitro groups.

4.2.5. Reactions Involving the Trifluoromethyl Group

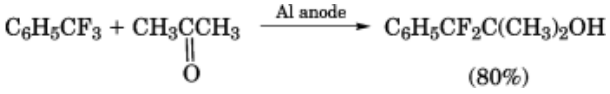
Aluminum chloride effects chlorinolysis of benzotrifluoride to give benzotrichloride (307). High yields of volatile acid fluorides are formed from benzotrifluoride and perfluorocarboxylic acids (308).



4,4′-Difluorobenzophenone, the key precursor to PEEK high performance resins, can be prepared by sequential (*1*) Friedel-Crafts coupling of 3,4-dichlorobenzotrifluoride, (*2*) exchange fluorination using $KF/CH_3SO_2CH_3$, and (*3*) reductive dechlorination with HCOONa/Pd-C (309).



Electroreductive coupling of benzotrifluorides with sacrificial aluminum or magnesium anodes in the presence of acetone, carbon dioxide, or *N,N*-dimethylformamide provides a novel route to $ArCF_2$-derivatives (310).



4.2.6. Biotransformation

Enzymatic oxidation of benzotrifluoride forms 3-trifluoromethyl-*cis*-1,2-dihydrocatechol; dehydration (acid pH) provides a novel route to 3-hydroxybenzotrifluoride [98-17-9] (171).

Table 8. Physical Properties of Benzotrifluoride[a]

Property	Value
mol wt	146.11
color	colorless
melting point, °C	−29.02
boiling point, °C	102.05
density, 25°C, g/mL	1.1814
coefficient of expansion (30–40°C)	0.00121
refractive index, n_D^{25}	1.4114
viscosity, mPa·s(= cP)	
38°C	0.488
99°C	0.282
surface tension, mN/m(=dyn/cm)	
20°C	23.39
latent heat of fusion, J/mol[b]	13,782.1
latent heat of vaporization, 102.05°C	
J/mol[b]	32.635.2
specific conductivity at 25°C, S/cm	1×10^{-7}
dielectric constant, 30°C	9.18
dipole moment, C·m[c]	8.54×10^{-30}
heat of combustion, J/g[b]	23,064.3
heat of formation, kJ/mol[b]	
vapor	−580.7
liquid	−618.4
boiling point of binary azeotrope, °C with 96.7 mol % bromine	58.1
solubility in water, g/100 g at room temperature	0.045
flash point (Cleveland open cup), °C[d]	15.6
fire point (Cleveland open cup), °C[d]	15.6
vapor pressure, in °C and kPa[e]	Antoine equation[f]

[a]Other properties of this compound and its derivatives have been reviewed (311).
[b]To convert J to cal, divide by 4.184.
[c]To convert $\mathrm{C{\cdot}m}$ to debye (D), divide by 3.336×10^{-30}.
[d]Ref. 312.
[e]To convert kPa to mm Hg, multiply by 7.5; $\mathrm{logkPa} = \mathrm{logmm\ Hg} - 0.875$.

[f] $\mathrm{Log}_{10}P = 6.0939 - \dfrac{1305.509}{(t + 217.280)}$.

4.3. Benzotrifluoride

Benzotrifluoride [98-08-8] (α,α,α-trifluorotoluene), $C_6H_5CF_3$ (mol wt, 146.11), is a colorless liquid (Table 8). Toxicity: oral (rat), LD_{50}, 1500 mg/kg; oral (mouse), LD_{LO}, 10,000 mg/kg; subcutaneous (frog), LD_{LO}, 870 mg/kg; intraperitoneal (mouse), LD_{LO}, 100 mg/kg (127).

Benzotrifluoride was first synthesized in 1898 via the reaction of benzotrichloride and antimony trifluoride (313). Benzotrifluoride can be produced by the high pressure reaction of benzotrichloride with anhydrous hydrogen fluoride (AHF). Typical conditions include a 4:1 AHF–benzotrichloride mole ratio at 80–110°C and 1.52–1.55 MPa (220–225 psi) for 2–3 h to give 70–75% yields of benzotrifluoride (314, 315). The pressure fluorination can be performed continuously in a series of autoclaves (316) or through a nickel reaction tube at 90–130°C at 3–5 MPa (435–725 psi) (317). Batch liquid-phase catalyzed processes at atmospheric pressure (318, 319) and continuous processes have been developed (320). High temperature vapor-phase fluorination processes have also been described (321).

Table 9. Properties of Benzotrifluoride Derivatives

Component	CAS Registry Number	Mol wt	Mp, °C	Bp, $°C_{kPa}$[a]	Refractive index n_D^t	Specific gravity, d_4^t	Flash point,[b] °C	Toxicity, LD_{50}
				Aminobenzotrifluoride				
$H_2NC_6H_4CF_3$								
2-aminobenzotrifluoride	[88-17-5]	116.13	34	$174–175_{100.4}$	1.4800^{25}	1.290^{25}	55	
3-aminobenzotrifluoride	[98-16-3]	116.13	5–6	$187–188$ $86_{2.67}$	1.4788^{20}	1.305^{25}	85	440[c] 690[d,e] 220[f]
				Monochlorobenzotrifluorides				
$CF_3C_6H_4Cl$								
2-chlorobenzotrifluoride	[88-16-4]	180.56		152.5	1.4550^{20}	1.367^{20}	98	
4-chlorobenzotrifluoride	[98-15-7]	180.56	−36	139 $29.5_{1.33}$	1.4444^{25}	1.338^{25}	110	>6.8[g] >2.7[h]
				Dichlorobenzotrifluorides				
$CF_3C_6H_3Cl_2$								
2,4-dichlorobenzotrifluoride	[320-60-5]	215.00	−26	177.5	1.4793^{25}	$1.501^{15.5}$	72	
3,4-dichlorobenzotrifluoride	[328-84-7]	215.00	−12.4	173.5	1.4736^{25}	1.478^{25}	65	2900[i] >2[j]

[a] To convert kPa to mm Hg, multiply by 7.5.
[b] Closed cup (ASTM procedure D3278).
[c] Inhalation (rat), LC_{50} mg/m^3 for 4 h (127).
[d] Inhalation (mouse), g/m^3 for 2 h (127).
[e] LC_{50}.
[f] Oral (mouse), mg/kg (127).
[g] Acute oral (rat), g/kg (323).
[h] Acute dermal (rabbit), g/kg (323).
[i] Acute oral (rat), mg/kg (324).
[j] Acute dermal (rabbit), g/kg (324).

4.4. Benzotrifluoride Derivatives

Laboratory recipes for 45 benzotrifluorides have been published (322). Physical properties and toxicity of commercially significant benzotrifluoride derivatives are listed in Table 9; the amino compounds are colorless to yellow and other derivatives are colorless.

4.4.1. 2-Chlorobenzotrifluoride

This compound is produced from 2-chlorobenzotrichloride and anhydrous hydrogen fluoride under atmospheric or high pressure conditions. Nitration forms 2-chloro-5-nitrobenzotrifluoride [777-37-7], a dye and germicide precursor.

4.4.2. 4-Chlorobenzotrifluoride

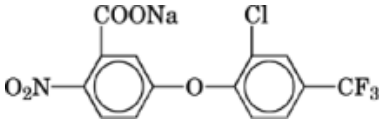
This isomer is produced from 4-chlorobenzotrichloride and anhydrous hydrogen fluoride. Nitration provides either 4-chloro-3-nitrobenzotrifluoride [121-17-5] (one-step) or 4-chloro-3,5-dinitrobenzotrifluoride [393-75-9] (two-step) for use in crop protection applications. Dinitration can also be accomplished in one step (85% yield) with 90% nitric acid/20% oleum (325). Single-step dehalogenation-reduction of 4-chloro-3,5-dinitrobenzotrifluoride provides a 96% yield of 3,5-diaminobenzotrifluoride [368-53-6] (326), an intermediate to specialty polymers.

4.4.3. 2,4-Dichlorobenzotrifluoride

This dichloro compound is produced from 2,4-dichlorobenzotrichloride and hydrogen fluoride. One commercial application is the manufacture of the pre-emergent herbicide, dinitramine [29091-05-2].

4.4.4. 3,4-Dichlorobenzotrifluoride

This compound is produced by chlorination of 4-chlorobenzotrifluoride and exhibits sufficient activation to undergo nucleophilic displacement with phenols to form diaryl ether herbicides, eg, acifluorofen sodium [62476-59-9].



4.4.5. 3-Aminobenzotrifluoride

The standard manufacturing route to 3-aminobenzotrifluoride involves nitration of benzotrifluoride to 3-nitrobenzotrifluoride [98-46-4], followed by hydrogenation. A comprehensive study on materials of construction to minimize corrosion during catalytic hydrogenation led to the recommendation of Cr–Ni–Mo steel (with $\geq$3% Mo) (327). Gas chromatographic details for monitoring this two-step process have been described (328), as well as analytical methods for assay of the 2- and 4-isomer impurities in 3-aminobenzotrifluoride (329). Environmental aspects of the manufacture of this product in Germany have been published (330). A novel process based on the one-step *in situ* fluorination-reduction of 3-nitrobenzotrichloride with ammonium bifluoride–hydrogen fluoride has been described (331, 332).

The amine group of 3-aminobenzotrifluoride can be replaced by Cl, Br, I, F, CN, or OH groups by standard diazotization reactions. Phosgenation gives 3-trifluoromethylphenylisocyanate [329-01-1], which can then be converted to the selective herbicide fluometuron [2164-17-2], a substituted urea.

4.5. Application

4.5.1. Crop Protection Chemicals

Benzotrifluoride derivatives have gained wide acceptance as herbicides, insecticides, and fungicides (Table 10).

Table 10. Benzotrifluoride Crop-Protection Chemicals

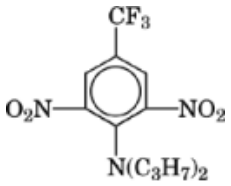
Common name	CAS Registry Number	Structure	Application
trifluralin	[1582-09-8]		pre-emergent herbicide

Table 10. ***Continued***

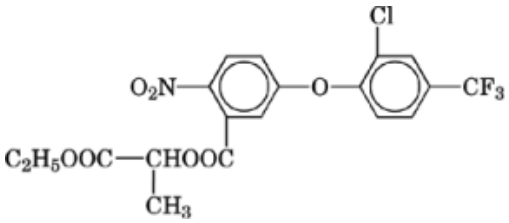
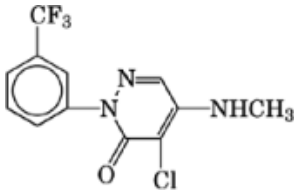
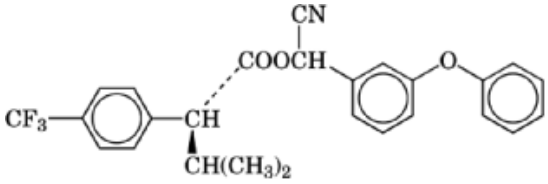
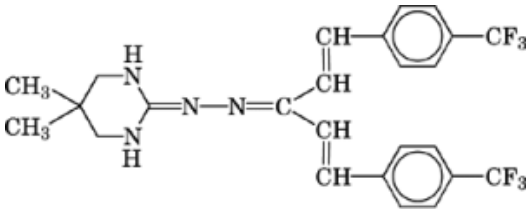
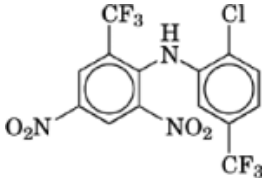
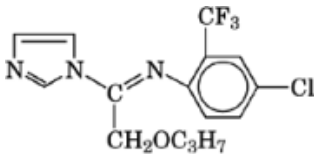
Common name	CAS Registry Number	Structure	Application
lactofen	[77501-63-4]		herbicide
norflurazon	[27314-13-2]		selective herbicide
fluvalinate	[69409-94-5]		insecticide
hydramethylnon	[67485-29-4]		insecticide
fentrifanil	[62441-54-7]		acaricide

Table 10. ***Continued***

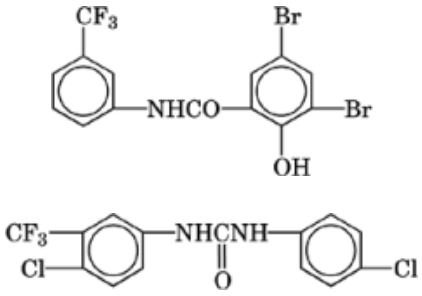
Common name	CAS Registry Number	Structure	Application
triflumizole	[68694-11-1]		fungicide

4.5.2. Drugs

Trifluoromethyl-based pharmaceuticals had been limited to phenothiazine tranquilizers and benzothiadiazine 1,1-dioxide diuretics (qv). However, new drugs have been developed (Table 11). One of the key properties of the CF_3 group is its high lipophilicity; it increases the lipid solubility of the pharmaceutical and thus accelerates absorption and transport within the host organism.

4.5.3. Germicides

Benzotrifluoride derivatives have also found wide use as antimicrobial agents in soaps, eg, the brominated and chlorinated materials, fluorosalan [4776-06-1] and cloflucarbon [369-77-7].



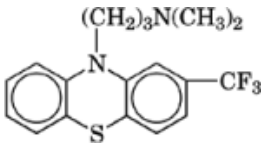
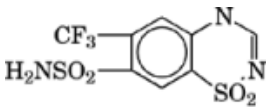
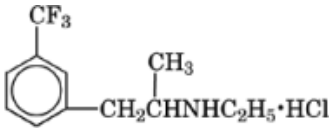
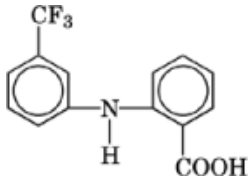
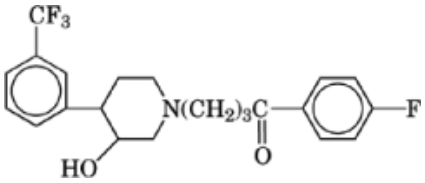
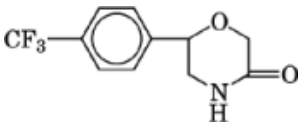
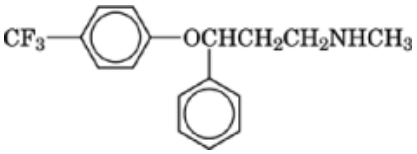
4.5.4. Other Biological Applications

4-Nitro-3-(trifluoromethyl)phenol [88-30-2] (TFM) is still employed by the Canadian Bureau of Fisheries and the U.S. Fish and Wildlife Service as a lampricide for the control of parasitic sea lamprey in the Great Lakes (see Aquaculture).

4.5.5. Dyes

Several reviews on fluorine-containing dyes have been published (333–335). The relative accessibility of benzotrifluorides has reflected the wide incorporation of the trifluoromethylphenyl group into azo, anthraquinone, and triphenylmethane dyes(qv). The trifluoromethyl group is claimed to improve the brightness, tinctorial values, and lightfastness of dyes. The electron-withdrawing effects of this group also tend to modify the absorption of light by a dye in the visible and uv region. In azo dyes (qv), aminobenzotrifluorides (Fast Base) are diazotized for subsequent coupling: 2-aminobenzotrifluoride CI Pigment Yellow 154 [88-17-5]; 3,5-bis(trifluoromethyl)aniline [328-74-5], CI Azoic Diazo Component 16; 2-amino-5-chlorobenzotrifluoride [445-03-4], CI Azoic Diazo Component 17; 3-amino-4-ethylsulfonylbenzotrifluoride [382-85-4], CI Azoic

Table 11. Benzotrifluoride Drugs

Common name	CAS Registry Number	Structure	Application
trifluprom azine	[146-54-3]		tranquilizer
flumethiazide	[148-56-1]		diuretic
fenfluramine	[404-82-0]		anorexigen
flufenamic acid	[53-78-9]		analgesic
trifluperidol	[749-13-3]		tranquilizer
flumetramide	[7125-73-7]		muscle relaxant
fluoxetine	[54910-89-3]		antidepressant

Diazo Component 19; and 3-amino-4-chlorobenzotrifluoride, CI Azoic Diazo Component 49 [121-50-6]. 3-Trifluoromethylbenzoyl halides are used to make anthraquinone vat dyes, eg, Indanthrene blue CLB [6942-78-0] (see Dyes, anthraquinone).

4.5.6. Miscellaneous Applications

Benzotrifluoride derivatives have been incorporated into polymers for different applications. 2,4-Dichlorobenzotrifluoride or 2,3,5,6-tetrafluorobenzotrifluoride [651-80-9] have been condensed with bisphenol A [80-05-7] to give benzotrifluoride aryl ether semipermeable gas membranes (336, 337). 3,5-Diaminobenzotrifluoride [368-53-6] and aromatic dianhydrides form polyimide resins for high temperature composites(qv) and adhesives (qv), as well as in the electronics industry (338, 339).

Photoresist applications in the microelectronics industry have also been disclosed (340). Thermally stable benzyl sulfonate esters based on 2-methyl-3-nitrobenzotrifluoride [6656-49-1] can serve as nonionic photoacid generators to promote a cascade of reactions during irradiation of the resist.

Liquid crystal applications include esters based on *m*- or *p*-hydroxybenzotrifluoride (341, 342), hydroxytrifluoromethylbiphenyls (343) or hydroxytrifluoromethylphenyl Schiff bases (344).

Inorganic analytical applications for benzotrifluoride derivatives include sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (Kobayashi's reagent) (345), and 4-(2,6-dinitro-4-trifluoromethylphenyl)aminobenzo-15-crown-5 (modified Takagi reagent (346).

Benzotrifluoride has been recommended as a fuel additive for internal combustion engines (347).

5. Arylfluoroalkyl Ethers

α,α,α-Trifluoromethoxybenzene [456-55-3], $C_6H_5OCF_3$, and other arylfluoroalkyl ethers and thioethers (HCF_2O-, HCF_2CF_2O-, CF_3CH_2O-, and CF_3S-), are assuming greater importance as crop-protection chemicals and pharmaceuticals.

5.1. Properties

The trifluoromethoxy (CF_3O-) group in $ArOCF_3$ exhibits unusual stability to strong acids and bases (including organometallic reagents), as well as to strong oxidizing and reducing conditions (348). The thermal stability is exceptional; extensive degradation in the gas phase was not observed (mass spectroscopy) in a sealed nickel tube until 600°C (348). Nuclear chlorinated trifluoromethoxy and bis(trifluoromethoxy)benzenes have exhibited moderate thermal stability for use in transformers and Rankine cycle engines (349).

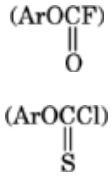
5.1.1. Reactions

The CF_3O- group exerts predominant para orientation in electrophilic substitution reactions such as nitration, halogenation, acylation, and alkylation (350).

5.2. Trifluoromethoxybenzenes ($ArOCF_3$)

Trifluoromethoxybenzene (α,α,α-trifluoroanisole, phenyl trifluoromethyl ether [456-55-3]), $C_6H_5OCF_3$ (mol wt 162.11), is a colorless liquid, bp 102°C, mp −50°C, n^{20}_D 1.4060, d^{25}_4 1.226, flash point (closed cup), 12°C.

Depending on the ring substituent, trifluoromethoxybenzenes can be made by the sequential chlorination–fluorination of anisole(s) (351–354). A one-step process with commercial potential is the BF_3 (or SbF_3)-catalyzed reaction of phenol with carbon tetrachloride/hydrogen fluoride (355). Aryl trifluoromethyl ethers, which may not be accessible by the above routes,may be made by fluorination of aryl fluoroformates or aryl chlorothioformates with sulfur tetrafluoride (348) or molybdenum hexafluoride (356).



5.3. Trifluoromethylthioaromatics ($ArSCF_3$)

Trifluoromethylthioaromatics (aryl trifluoromethyl sulfides) can be made by sequential chlorination–fluorination (SbF_3 or HF) of the corresponding thioanisole (351, 357). In the case of 4-trifluoromethylmercaptophenol [825-83-2], $4\text{-}CF_3C_6H_4SH$, used for the production of the coccidiostat toltrazuril [69004-03-1] (Table 12), protection of the phenolic group as the carbonate ester is required prior to chlorination (358). Coupling of aryl halides with trifluoromethylthiocopper, CF_3SCu, provides an alternative entry to trifluoromethylthioaromatics (359, 360).

5.4. Difluoromethoxyaromatics ($ArOCHF_2$) and Sulfur Analogues ($ArSCHF_2$)

Difluoromethyltion of phenol (or thiophenols) with chlorodifluoromethane, $CHClF_2$, and aqueous caustic in dioxane gives good yields of aryldifluoromethyl ethers (361). A modification features the use of phase-transfer catalysts such as tris(3,6-dioxaheptyl)amine (TDA-1) (362).

Table 12. Aryl Fluoroalkyl Ether Applications

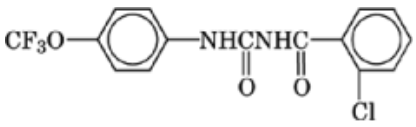
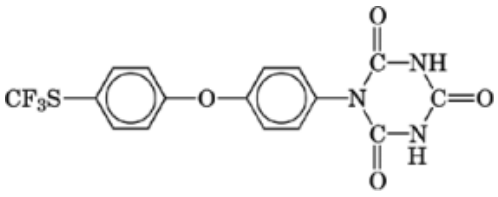
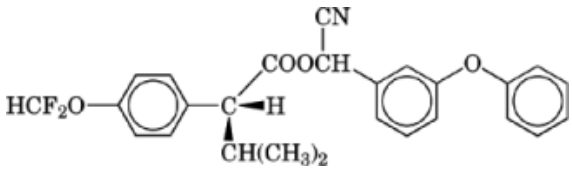
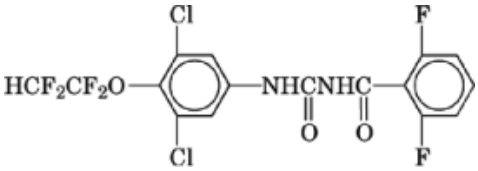
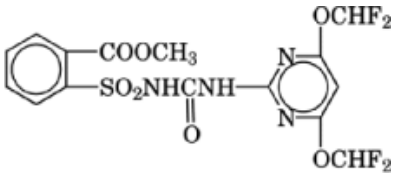
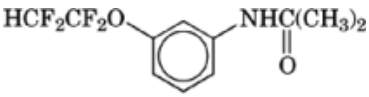
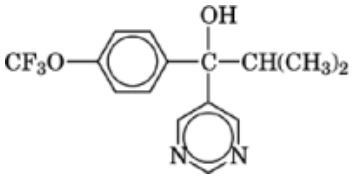
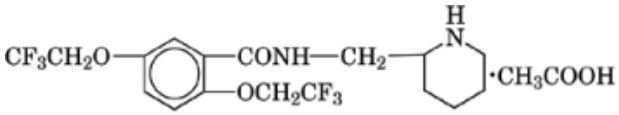
Common name	CAS Registry Number	Structure
		Insecticides
triflumuron	[64628-44-0]	
toltrazuril[a]	[69004-03-1]	
flucythrinate	[70124-77-5]	

Table 12. ***Continued***

Common name	CAS Registry Number	Structure
hexaflumuron	[86479-06-3]	
		Herbicides
primsulfuronmethyl	[86209-51-0]	
tetrafluron	[27954-37-6]	
		Other
flurprimidol[b]	[56425-91-3]	
flecainide acetate[c]	[54143-56-5]	

[a] Coccidiostat.
[b] Plant growth regulator.
[c] Cardiac depressant.

5.5. Tetrafluoroethoxyaromatics ($ArOCF_2CF_2H$)

Tetrafluoroethoxyaromatics are produced by base-catalyzed addition of tetrafluoroethylene to phenols (348, 363).

5.6. Aryltrifluoroethyl Ethers ($ArOCH_2CF_3$)

2,2,2-Trifluoroethoxybenzenes are obtained from the reaction of activated haloaromatics with sodium 2,2,2-trifluoroethoxide in polar solvents (364); phase-transfer catalysts are also employed (365). Nitro groups can also be displaced by the fluoroalkylation technique, eg, 4-nitrobenzonitrile was converted to 4-(2,2,2-trifluoroethoxy)benzonitrile (366). Trifluoroethoxybenzene pharmaceutical intermediates can be prepared by the base-catalyzed reaction of 2,2,2-trifluoroethyl trifluoromethanesulfonate (a trifluorethyl-transfer agent), $CF_3SO_3CH_2CF_3$, with phenols (367).

5.7. Applications

Table 12 lists crop-protection chemicals and pharmaceuticals containing the aryl fluoroalkyl ether group. Trifluoromethoxybenzene ($ArOCF_3$) derivatives (186, 187) and related arylfluoroalkyl ethers, $ArO(CH_2)_nR_f$ ($n = 1 - 6$) (368, 369) are of use in liquid crystal applications.

6. Fluorinated Nitrogen Heterocyclics

Ring- or side-chain fluorinated nitrogen heterocyclics have been incorporated into crop-protection chemicals, drugs, and reactive dyestuffs. Key intermediates include fluorinated pyridines, quinolines, pyrimidines, and triazines. Physical properties of some fluorinated nitrogen heterocyclics are listed in Table 13.

6.1. Ring-Fluorinated Pyridines

Exchange fluorination of chloropyridines is the principal tool for production of ring-fluorinated pyridines. Diazotization of aminopyridines in pyridine–hydrogen fluoride (Olah's reagent) (370) or ammonium fluoride–hydrogen fluoride (371) has also been used. An emerging synthesis tool is the use of fluorinated aliphatic building blocks to make fluoropyridines. Early studies on the substitutive fluorination (F_2) of pyridine gave 2-fluoropyridine in low yields and posed severe reaction hazards (372, 373). Modifications featuring low temperature fluorination of substituted pyridines (alkyl, halogen, ester, or ketone functions) in 1,1,2-trichloro-1,2,2-trifluoroethane, $CF_2ClCFCl_2$, solvent give good yields of the corresponding 2-fluoropyridine (374, 375). Tamed fluorine reagents such as xenon difluoride (376) and cesium fluoroxysulfate (377) can also fluorinate pyridine. A promising substitutive fluorination technique is the base-catalyzed decomposition of *N*-fluoropyridinium salts, BF^-_4, PF^-_6, or SbF^-_6, to give high yields of the substituted 2-fluoropyridine (378). The salt is made in 80% yield; the decomposition yields 72–91% of product.

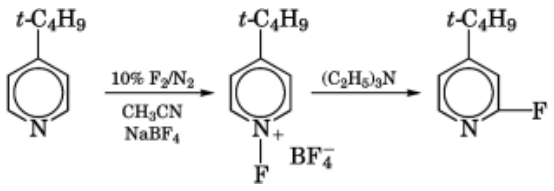


Table 13. Properties of Miscellaneous Fluorinated Heterocyclic Compounds

Component	CAS Registry Number	Mol wt	Mp, °C	Bp, °C/kPa[a]	Refractive index, n_D^t	Specific gravity, d_4^t	Flash point, °C
			Fluoropyridines				
C_5H_4FN							
2-fluoropyridine	[372-48-5]	97.09		$126_{100.4}$	1.4678^{20}	1.1281^{20}	24[b]
3-fluoropyridine	[372-47-4]	97.09		105–$107_{100.3}$	1.4700^{20}	1.125^{25}	13[b]
4-fluoropyridine	[694-52-0]	97.09	100[c]	$108_{100.0}$	1.4730^{20}		
$C_5H_3F_2N$							
2,4-difluoropyridine	[3491-90-7]	115.08	134–135[c]	104–105			
2,6-difluoropyridine	[1513-65-1]	115.08		$124.5_{99.1}$	1.4349^{25}	1.265^{25}	32[b]
$C_5H_2F_3N$							
2,4,6-trifluoropyridine	[3512-17-2]	133.07		94–95			
C_5HF_4N							
2,3,5,6-tetrafluoropyridine	[2875-18-5]	151.06		102			
C_5H_5N[d]							
pentafluoropyridine	[70-16-3]	169.05	−41.5	83.3	1.3856^{20}		
			Perfluoroalkylpyridines				
2-trifluoromethylpyridine	[368-48-9]	147.10		$143_{99.4}$	1.4144^{25}		
3-trifluoromethylpyridine	[3796-23-4]	147.10		113–115	1.4150^{25}		
4-trifluoromethylpyridine	[3796-24-5]	147.10		108–110	1.4144^{25}		
2-chloro-5-trifluoromethylpyridine	[52334-81-3]	181.55	32–34	152_{100}		1.417^{20}	110[e]
			Fluoropyrimidines				
2,4,6-trifluoropyrimidine	[696-82-2]	134.06		$98;60_{24}$	1.4015^{25}		
2,4,5,6-tetrafluoropyrimidine	[767-79-3]	152.06		89	1.3875^{25}		
5-chloro-2,4,6-trifluoropyrimidine	[697-83-6]	168.51		114.5	1.4390^{20}		
			Fluorotriazines				
2,4,6-trifluoro-1,3,5-triazine	[675-14-9]	135.05	−38	$72.4_{101.67}$	1.3844^{24}	1.60^{25}	
2,4,6-*tris*-(trifluoromethyl)-1,3,5-triazine	[368-66-1]	285.07	−24.8	95–96	1.3161^{25}	1.593^{25}	

[a] To convert kPa to mm Hg, multiply by 7.5.
[b] Tag closed cup.
[c] Mp of HCl salt.
[d] Trouton's constant, 24.9; latent heat of vaporization, 36, 338 J/mol.
[e] Closed cup (ASTM procedure D3278).

6.2. Monofluoropyridines

6.2.1. 2-Fluoropyridine

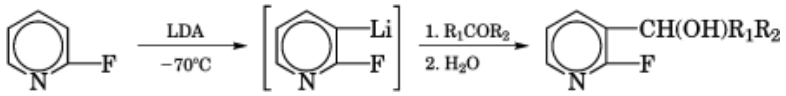
Diazotization of 2-aminopyridine in anhydrous hydrogen fluoride forms 2-fluoropyridine in high yield (178, 370). Modifications include fluorodediazonization of substituted 2-aminopyridines in ammonium fluoride–hydrogen fluoride (371) or pyridine–hydrogen fluoride (370) media. Exchange-fluorination of 2-chloropyridine with potassium fluoride in polar solvents is sluggish (210°C for 21 d; 50–58% yield) (379). The solvent-free exchange-fluorination employing potassium bifluoride (KHF_2) and 2-chloropyridine (315°C/4 h) gave 2-fluoropyridine in 74% yield (380). A new development features exchange fluorination of 2-chloropyridine with hydrogen fluoride–γ-collidine at 150–200°C to give 94% yield of product (381).

Fluorine at the 2 position ($pK_a = -0.44$) significantly reduces pyridine ($pK_a = 5.17$) basicity more than at the 3 position ($pK_a = 2.97$) (382). 2-Fluoropyridine is readily hydrolyzed to 2-pyridone in 60% yield by reflux in 6 *N* hydrochloric acid (383). It is quite reactive with nucleophiles. For example, the halogen mobility ratio from the comparative methoxydehalogenation of 2-fluoropyridine and 2-chloropyridine was 85.5/1 at 99.5°C

(384). This lability of fluorine has been utilized to prepare fluorine-free *O*-2-pyridyl oximes of 3-oxo steroids from 2-fluoropyridine for possible use as antifertility agents (385).

2-Fluoropyridine is a useful reagent for synthetic applications. It reacts with methyl *p*-toluenesulfonate to give 1-methyl-2-fluoropyridinium *p*-toluenesulfonate [58086-67-2] (Mukaiyama's reagent). Such onium salts are used in the oxidation of alcohols, cross-coupling of Grignard reagents, Beckmann rearrangements of ketoximes, nonenzymatic biogenetic-like synthesis of terpenes (386), and preparation of new synthetic penicillins (387).

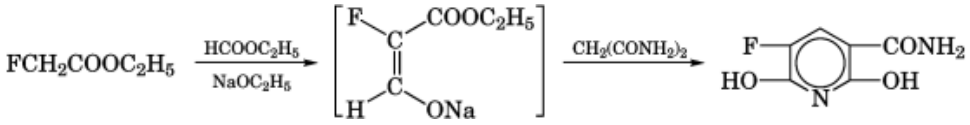
Metallation of 2-fluoropyridine with lithium diisopropylamide (LDA) gives 2-fluoro-3-lithiopyridine, thereby providing entry to 3-substituted pyridines (388). This technique has been used to make fluorine analogues of the antitumor ellipticines (389).



6.2.2. 3-Fluoropyridine

Diazotization of 3-aminopyridine(s) in hydrogen fluoride (390), pyridine–hydrogen fluoride (370), or ammonium fluoride–hydrogen fluoride (371) can be effected in good yield. 3-Fluoropyridine can also be made by the Balz-Schiemann technique in 50% yield. Earlier warnings concerning the instability of 3-pyridyldiazonium fluoroborate (391) were confirmed by later reports on detonations involving this salt (392). Related compounds such as 2-chloro-3-pyridyldiazonium fluoroborate also decomposed with explosive violence (393).

3-Fluoropyridine derivatives can be constructed from fluoroaliphatic feedstocks. 5-Fluoro-2,6-dihydroxynicotinamide [655-13-0], a precursor to the anti-bacterial, enoxacin [74011-58-8], was prepared in 63% yield from ethyl fluoroacetate [459-72-3], ethyl formate [109-94-4], and malonamide [108-13-4] (394).



A complementary cyclization technique based on dichlorofluoroacetonitrile [83620-05-7], $FCCl_2CN$, was employed to form 2-chloro-3-fluoro-5-methylpyridine [34552-15-3] (395).

Derivatives such as 3-fluoro-4-nitropyridine [13505-01-6] (396) or the 1-oxide [769-54-0] (397) have been used to characterize amino acids and peptides. 5-Fluoro-3-pyridinemethanol [22620-32-2] has been patented as an antilipolytic agent (398). A promising antidepressant, 1-(3-fluoro-2-pyridyl)piperazine hydrochloride [85386-84-1] is based on 2-chloro-3-fluoropyridine [17282-04-1] (399).

6.2.3. 4-Fluoropyridine

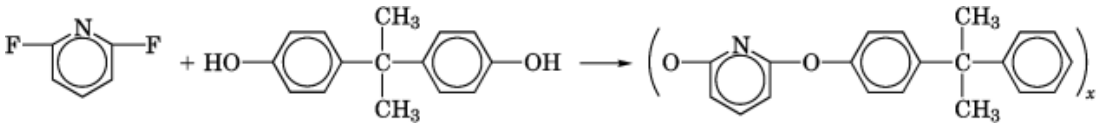
This isomer can be prepared in 54–81% yield by diazotization of 4-aminopyridine in anhydrous hydrogen fluoride (370, 371, 400). Free 4-fluoropyridine readily undergoes self-quaternization to give pyridyl pyridinium salts (401); stabilization can be effected as the hydrochloride salt (371, 400). Numerous 4-fluoropyridinium salts, eg, 4-fluoro-1-methylpyridinium iodide, have been converted to novel penicillins (387, 402).

6.3. Difluoropyridines

2,4-Difluoropyridine can be prepared (26% yield) from 2,4-dichloropyridine and potassium fluoride in sulfolane and ethylene glycol initiator (403). The 4-fluorine is preferentially replaced by oxygen nucleophiles to give 2-fluoro-4-hydroxypyridine derivatives for herbicidal applications (404).

Fluorination of 2,6-diaminopyridine in anhydrous hydrogen fluoride gave a 62% yield of 2,6-difluoropyridine (26, 371, 405). 2,6-Difluoropyridine is also prepared in 52% yield (200°C, 100 h) from 2,6-dichloropyridine and potassium fluoride in dimethyl sulfone or sulfolane (406). The reaction can be performed in dimethyl sulfoxide with shorter reaction times (9 h, 186°C) (407); addition of tetramethylammonium chloride (TMAC) catalyst lowers reaction temperature to 150°C, thereby minimizing solvent degradation (408). Solvent-free exchange-fluorination (KF) at 400°C (16 h) gave 80% yield of 2,6-difluoropyridine which attests to its high thermal stability (409).

Displacement reactions with oxygen nucleophiles are of potential commercial interest. Alkaline hydrolysis provides 2-fluoro-6-hydroxypyridine [55758-32-2], a precursor to 6-fluoropyridyl phosphorus ester insecticides (410–412). Other oxygen nucleophiles such as bisphenol A and hydroquinone have been used to form aryl–pyridine copolymers (413).



Nitration with mixed nitric and sulfuric acids provides 79% yield of 3-nitro-2,6-difluoropyridine [5860-02-1], bp 218–220°C (414).

3-Bromo or chloro-2,6-difluoropyridines can be prepared in 50% yield by diazotization of the corresponding 3-halo-2,6-diaminopyridine in ammonium fluoride–hydrogen fluoride solvent (371). 5-Chloro-2,3-difluoropyridine [89402-43-7], a precursor to the herbicide pyroxofop [105512-06-9], was synthesized by a multistep sequence based on allyl chlorodifluoroacetate [118337-48-7], $ClCF_2CO_2\text{-}CH_2CH{=}CH_2$ (415).

6.4. Tri-, Tetra-, and Pentafluoropyridines

2,4,6-Trifluoropyridine can be prepared in 75% yield by catalytic hydrogenolysis (palladium-on-carbon, 280°C) of 3,5-dichloro-2,4,6-trifluoropyridine [1737-93-5] (416). The latter is synthesized by exchange fluorination of pentachloropyridine with potassium fluoride in polar solvents such as *N*-methylpyrrolidinone (417, 418). 3,5-Dichloro-2,4,6-trifluoropyridine is used to prepare the herbicides haloxydine [2693-61-0] and fluroxypyr-(1-methylheptyl) [81406-37-3].

2,3,5,6-Tetrafluoropyridine can be prepared in 75% yield from the hydrogenation of pentafluoropyridine under free-radical (catalytic) or nucleophilic (lithium aluminum hydride) conditions (416, 419). No practical uses for 2,3,5,6-tetrafluoropyridine are known.

Pentafluoropyridine was first synthesized in 1960 in 27% yield by the defluorination of undecafluoropiperidine (prepared in low yield by the electrochemical fluorination of pyridine) over a nickel or iron surface at 560–610°C (420, 421). The preferred route is the solvent-free exchange-fluorination (KF) of pentachloropyridine at 480–500°C to give 69–83% yields of pentafluoropyridine (418, 422). Pentafluoropyridine is a weak base, does not form a hydrochloride salt, and is more volatile (bp 83.3°C) than pyridine (bp 115°C). Pentafluoropyridine readily undergoes reaction with nucleophilic agents to give 4-substituted-2,3,5,6-tetrafluoropyridines. More than 30 examples of these 4-substitution reactions have been compiled (423). Derivatives of 4-hydroxytetrafluoropyridine [2693-66-5] and related compounds exhibit herbicidal properties (424, 425).

The nucleophilic equivalent of the Friedel-Crafts reaction of pentafluoropyridine with hexafluoropropene–potassium fluoride in sulfolane gave perfluoro-(4-isopropyl)pyridine in 94% yield (426).

Pentafluoropyridine–hexafluorobenzene working fluids show the requisite stability at 382°C for automotive Rankine-cycle power units (427). Hydroxyl and related functions in steroids can be selectively protected as tetrafluoro-4-pyridyl ethers by pentafluoropyridine (428).

6.5. Applications

Until recently, haloxydine, a herbicide, was one of the few early examples of crop-protection chemicals containing ring-fluorinated pyridines. Fluroxypyr-(1-methylheptyl) and pyroxofop are new herbicides that are being commercialized (Table 14).

Several 3-fluoropyridine derivatives are employed to produce enoxacin, tosufloxacin, and other naphthyridine antibacterials (Table 14). Examples of such intermediates include 2,6-dichloro-5-fluoronicotinonitrile (429), ethyl 2,6-dichloro-5-fluoronicotinate (430), 2-chloro-3-fluoropyridine (393), 6-acetyl-2-(4-acetyl-1-piperazinyl)-3-fluoropyridine (431), and 5-fluoro-2,6-dihydroxynicotinamide (394).

6.6. Perfluoroalkylpyridines

New developments in trifluoromethylpyridine technology are associated with the commercialization of numerous crop-protection chemicals as herbicides, fungicides, and insecticides (Table 15). Physical properties for representative trifluoromethylpyridines are listed in Table 13.

The standard synthesis method features side-chain chlorination of a methylpyridine (picoline), followed by exchange-fluorination with hydrogen fluoride or antimony fluorides (432, 433). The fluorination of pyridinecarboxylic acids by sulfur tetrafluoride (434) or molybdenum hexafluoride (435) is of limited value for high volume production operations due to high cost of fluorinating agent.

A significant development in trifluoromethylpyridine synthesis strategy is the use of fluorinated aliphatic feedstocks for the ring-construction sequence. Examples include the manufacture of the herbicide dithiopyr, utilizing ethyl 4,4,4-trifluoroacetoacetate [372-31-6], $CF_3COCH_2COOC_2H_5$ (436, 437). 2,3-Dichloro-5-trifluoromethylpyridine [69045-84-7], a precursor to several crop-protection chemicals (see Table 15), can be prepared by conversion of 1,1,1-trichloro-2,2,2-trifluoroethane [354-58-5], CF_3CCl_3, to 2,2-dichloro-3,3,3-trifluoropropionaldehyde [82107-24-2], CF_3CCl_2CHO, followed by cyclization with acrylonitrile [107-13-1] (415).

2-Trifluoromethylpyridine can be prepared in 54% yield from picolinic acid and sulfur tetrafluoride–hydrogen fluoride (434). 2-Trifluoromethylpyridine is a weak base; no hydrochloride salt is formed. However, 2-trifluoromethylpyridine 1-oxide [22253-71-0] (bp 132–133°C/2.7 kPa (20 mm Hg)) is prepared in 81% yield using 30% hydrogen peroxide–acetic acid (438).

3-Trifluoromethylpyridine can be prepared in 25–65% yield from nicotinic acid and sulfur tetrafluoride (434, 439). An alternative method is the passage of chlorine into a mixture of β-picoline and hydrogen fluoride in an autoclave (190°C, 3 MPa) (440). 4-Trifluoromethylpyridine is prepared in 57% yield from isonicotinic acid and sulfur tetrafluoride.

2-Chloro-5-trifluoromethylpyridine, an intermediate to the herbicide fluazilop–butyl, can be made from β-picoline by two processes. β-Picoline is chlorinated to 2-chloro-5-trichloromethylpyridine [69405-78-9], followed by fluorination with hydrogen fluoride under pressure (200°C, 10 h) (441) or vapor-phase (350°C, CCl_4 diluent) conditions (442). An alternative process features the single-step vapor-phase reaction of β-picoline with chlorine–hydrogen fluoride (400°C, N_2 or CCl_4 diluent) (443).

6.7. Fluoroquinolines

The standard routes to monofluoroquinolines have been the Balz-Schiemann reaction from the corresponding aminoquinoline or the Skraup reaction from glycerol and a fluoroaniline. Exchange-fluorination also has been used. 2-Chloroquinoline and potassium fluoride in dimethyl sulfone gave 60% yield of 2-fluoroquinoline [580-21-2], C_9H_5FN; bp 133°C at 4 kPa (30 mm Hg); 75°C at 0.3 kPa (2 mm Hg); n^{25}_D 1.5827 (406). Likewise, heptachloroquinoline and potassium fluoride at 470°C for 17 h gave a 71% yield of heptafluoroquinoline [13180-38-6], C_9F_7N; mp 95–95.5°C, bp 205°C (444).

Table 14. Applications of Ring-Fluorinated Pyridines

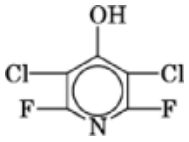
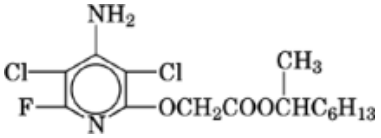
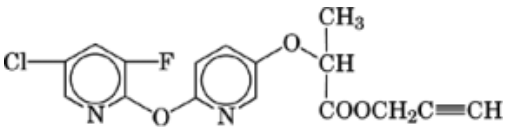
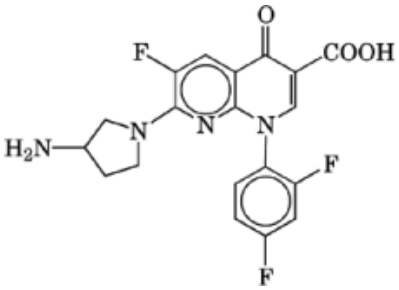
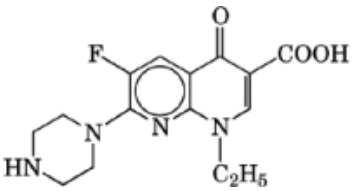
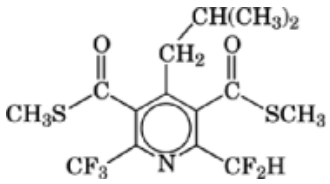
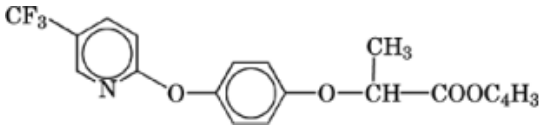
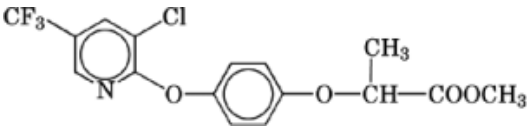
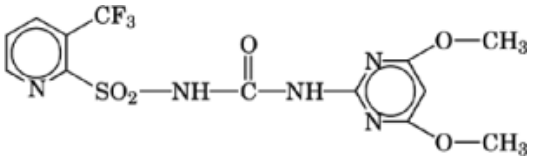
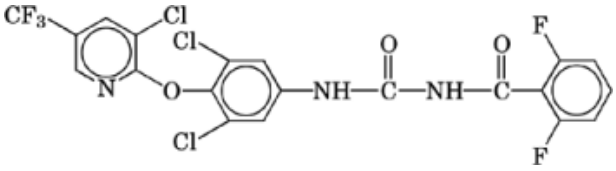
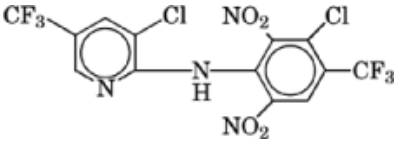
Common name	CAS Registry Number	Structure
	Herbicides	
haloxydine	[2693-61-0]	
fluroxypyr-(1-methylheptyl)	[81406-37-3]	
pyroxofop	[105512-06-9]	
	Antibacterials	
enoxacin	[74011-58-8]	
tosufloxacin	[108138-46-1]	

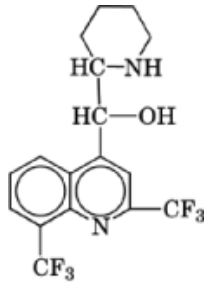
Table 15. Trifluoromethylpyridine-Based Crop-Protection Chemicals[a]

Common name	CAS Registry Number	Structure
dithiopyr	[97886-45-8]	
fluazilop–butyl	[69806-50-4]	
haloxyfop–methyl	[69806-40-2]	
flazasulfuron	[104040-78-0]	
chlorfluazuron[b]	[71422-67-8]	
fluazinam[c]	[79622-59-6]	

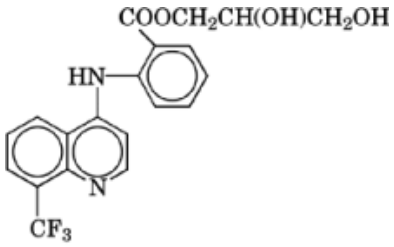
[a] Herbicide unless otherwise noted.
[b] Insecticide.
[c] Fungicide.

The main preparative techniques used to make all seven trifluoromethyl-quinoline isomers include copper-assisted coupling of the haloquinoline with trifluoromethyl iodide (112); quinolinecarboxylic acid with sulfur tetrafluoride–hydrogen fluoride (434, 445); and aminobenzotrifluoride and glycerol (Skraup reaction) (446, 447).

Commercial trifluoromethylquinoline-based products are mefloquine [53230-10-7], an antimalarial, and floctafenine [23779-99-9], an analgesic. The cyclization step to construct the 2,8-bis(trifluoromethyl)quinoline nucleus in mefloquine employs 2-aminobenzotrifluoride [88-17-5] and ethyl 4,4,4-trifluoroacetoacetate [372-31-6] (448).



mefloquine



floctafenine

6.8. Fluoroquinolones

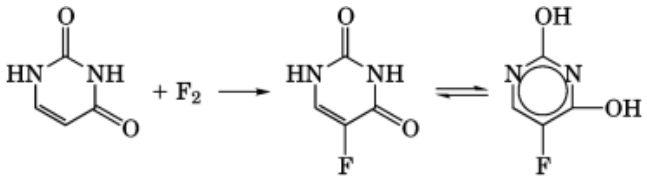
A primary development has been the rapid commercialization of fluoroquinolone antibacterials (427). The single-fluorinated quinolones (second generation) constitute 10% of the worldwide prescriptions for antibiotics: norfloxacin [70458-96-7], enoxacin [74011-58-8], perfloxacin [70458-92-3], ciprofloxacin [85721-33-1], and ofloxacin [82419-36-1] (449) (see Antibacterial agents, quinolones). Annual sales (1992) were estimated at $800 million. As new agents are introduced, fluoroquinolones are expected to maintain an average growth rate of 30% during the 1991–1997 time period (450). New synthesis strategy includes multiple-fluorinated quinolones (third generation) such as lomefloxacin [98079-51-7], fleroxacin [79660-72-3], temafloxacin hydrochloride [105784-61-0], and tosufloxacin [108138-46-1].

The discovery of new broad spectrum antibiotics has been accompanied by the development of processes for fluorinated feedstocks: ring-fluorinated aromatics for those quinolones containing a fluorobenzopyridone group, and fluorinated pyridine precursors for those antibiotics containing a naphthyridine nucleus (enoxacin, tosufloxacin) (see Table 14).

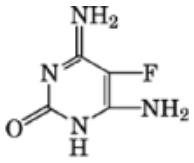
6.9. Fluoropyrimidines

Fluoropyrimidines find diverse use in cancer chemotherapy and other drug applications, as well as in fiber-reactive dyes. Table 13 lists physical properties of representative fluoropyrimidines.

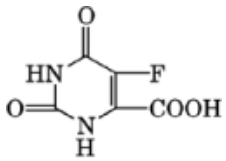
5-Fluoropyrimidine derivatives are of tremendous importance in cancer chemotherapy, eg, 5-fluorouracil [51-21-8] (5-FU). The original 5-fluorouracil process featured a multistep low yield route based on ethyl fluoroacetate (451). Direct fluorination (fluorine) of uracil [66-22-8] gives high yields of 5-FU (452–455). This process has now been commercialized.



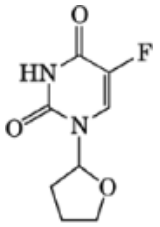
Other monofluoropyrimidines of biological interest are 5-fluorocytosine [2022-85-7], an antifungal agent; 2′-deoxy-5-fluorouridine [50-91-9] (5-FUDR), an antiviral and antineoplastic agent; 5-fluoroorotic acid [703-95-7] (5-FOA), used in yeast molecular genetics (456); and tegafur [17902-23-7] (Ftorafur), an antineoplastic agent which releases 5-FU *in vivo* (see Chemotherapeutics, anticancer).



5-fluorocytosine



5-FOA



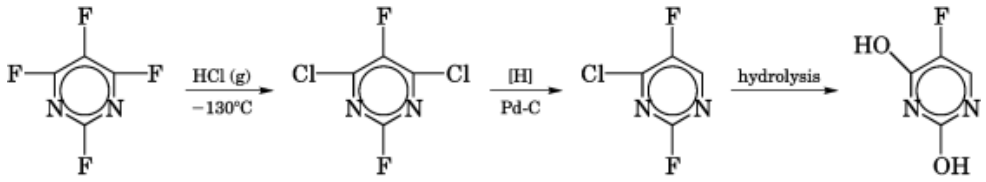
tegafur

Exchange fluorination is the main synthetic tool to prepare polyfluoropyrimidines. It was established that choice of fluorinating agent permits selectivity during exchange fluorination of nuclear- and side-chain chlorinated pyrimidines: NaF and KF fluorinate only in the heterocyclic nucleus; HF in the nucleus and in the chlorinated methyl group; and SbF_3 only in the chlorinated methyl group (457).

2,4,6-Trifluoropyrimidine can be prepared in 85% yield from 2,4,6-trichloropyrimidine [3764-01-0] and potassium fluoride in sulfolane or solvent-free conditions (458, 459). Derivatives such as 1,1,1-trichloro-3-[5-(2,4,6-trifluoropyrimidyl)]-3,4-epoxybutane [121058-68-2] have been prepared as potential herbicides (460).

2,4,5,6-Tetrafluoropyrimidine has been prepared by direct fluorination of 2,4,6-trifluoropyrimidine with silver difluoride in perfluorobutylamine solvent (461, 462). A more direct route (85% yield) is the reaction of tetrachloropyrimidine and potassium fluoride in an autoclave at 480°C for 42 h (463).

Tetrafluoropyrimidine was converted to the antineoplastic 5-fluorouracil (5-FU) by a novel process based on the sequence: partial exchange chlorination (61% yield), selective hydrogenolysis in triethylamine (71% yield) and hydrolysis (85–93% yield) (464).



5-Chloro-2,4,6-trifluoropyrimidine [697-83-6] has gained commercial importance for the production of fiber-reactive dyes (465, 466). It can be manufactured by partial fluorination of 2,3,5,6-tetrachloropyrimidine [1780-40-1] with anhydrous hydrogen fluoride (autoclave or vapor phase) (467) or sodium fluoride (autoclave, 300°C) (468). 5-Chloro-2,4,6-trifluoropyrimidine is condensed with amine chromophores to provide the 5-chloro-2,4-difluoropyrimidyl group; the fluorine atom of the latter then reacts with a nucleophilic site in the fabric. Commercial reactive dyes for cottons and cellulosics include Levafix EA and PA Dyestuffs and Drimarene K and R Dyestuffs. For wool, the following 5-chloro-2,4-difluoropyrimidyl reactive dyes are offered: Verofix Dyestuffs and Drimalene Dyestuffs (see Dyes, reactive).

6.10. Fluorotriazines

Ring-fluorinated triazines are used in fiber-reactive dyes. Perfluoroalkyl triazines are offered commercially as mass spectral markers and have been intensively evaluated for elastomer and hydraulic fluid applications. Physical properties of representative fluorotriazines are listed in Table 13. Toxicity data are available. For cyanuric fluoride, LD_{50} = 3.1 ppm for 4 h (inhalation, rat) and 160 mg/kg (skin, rabbit) (127).

6.11. 2,4,6-Trifluoro-1,3,5-Triazine

Cyanuric fluoride [675-14-9] can be produced from 2,4,6-trichloro-*s*-1,3,5-triazine [108-77-0] (cyanuric chloride) with hydrogen fluoride under autoclave (469, 470) or vapor-phase (471) conditions. Sodium fluoride (in sulfolane solvent) can also be used to manufacture cyanuric fluoride (472, 473).

Cyanuric fluoride is readily hydrolyzed to 2,4,6-trihydroxy-1,3,5-triazine [108-80-5] (cyanuric acid). Cyanuric fluoride reacts faster with nucleophilic agents such as ammonia and amines than cyanuric chloride.

Fiber-reactive dyes containing the fluorotriazinyl group are based on the condensation of chromophores containing amino groups with 6-substituted-2,4-difluorotriazines. The latter can be prepared from cyanuric fluoride or from the reaction of alkali metal fluorides with 6-substituted-2,4-dichlorotriazines. Comparative advantages of monofluorotriazinyl dyes over commercial monochlorotriazinyl analogues have been reviewed (466).

Cyanuric fluoride has been employed as a specific reagent for tyrosine residues in enzymes (474). Cyanuric fluoride can also serve as a fluorinating agent in fluorodehydroxylation reactions, eg, the conversion of 2-hydroxypyridine [142-08-5] to 2-fluoropyridine (475). This technique was subsequently extended to the preparation of acid fluorides from the corresponding carboxylic acid (476). It has found application in peptide synthesis from amino acids through the corresponding acid fluoride (477).

6.12. 2,4,6-tris-(Trifluoromethyl)-1,3,5-Triazine

This compound can be prepared by trimerization of trifluoroacetonitrile (478) or fluorination of 2,4,6-*tris*-(trichloromethyl)-1,3,5-triazine with hydrogen fluoride–antimony pentachloride or antimony trifluoride–antimony pentafluoride (479). LC_{50} = 1400 ppm for 4 h (inhalation, rat) (127).

tris-(Trifluoromethyl)-*s*-triazine [368-66-1], as well as the *tris*-perfluoroethyl [858-46-8], propyl [915-22-9], heptyl [21674-38-4], and nonyl [57104-59-4] *s*-triazines are commercially offered as mass spectrometry internal reference standards for a wide mass range, 285–1485. The perfluoroalkylene (perfluoroalkyl)-*s*-triazines and perfluoroalkylene(perfluoroalkyloxy)-*s*-triazines were found to be suitable nonflammable hydraulic fluids in the -25 to $+300^{\circ}C$ temperature range. Numerous laboratories have investigated the synthesis and properties of perfluoroalkylene elastomers containing the *s*-triazine functionality (480, 481).

6.13. Miscellaneous Fluorinated Nitrogen Heterocyclics

Two reviews (1981, 1990) include nitrogen heterocyclics not covered in the present survey (482, 483). The 1990 review dealing with four-, five-, and six-membered ring heterocyclic compounds emphasizes biological properties (482).

BIBLIOGRAPHY

"Fluorinated Aromatic Compounds" under "Fluorine Compounds, Organic," in *ECT* 2nd ed., Vol. 9, pp. 775–802, by A. K. Barbour, M. W. Buxton, and G. Fuller, Imperial Smelting Corp., Ltd.; in *ECT* 3rd ed., Vol. 10, pp. 901–936, by M. M. Boudakian, Olin Chemicals; "Perfluoroalkylene Triazines" under "Fluorine Compounds, Organic," *ECT* 3rd ed., Vol. 10, pp. 948–951, by W. R. Griffen, Air Force Materials Laboratory.

Cited Publications

1. M. R. Kilbourn, *Fluorine-18 Labeling of Radiopharmaceuticals*, National Academy Press, Washington, D.C., 1990.
2. G. Furin, in L. German and S. Zemskov, eds., *New Fluorinating Agents in Organic Synthesis*, Springer-Verlag, Berlin, 1989, Chapt. 9, p. 35.

3. V. Grakauskas, *J. Org. Chem.* **35**, 723 (1970); *Ibid.*, **34**, 2835 (1969).
4. N. B. Kaz'mina and co-workers, *Dokl. Akad. Nauk SSSR* **194**, 1329 (1970).
5. F. Cacace and co-workers, *J. Am. Chem. Soc.* **102**, 3511 (1980).
6. S. T. Purrington and D. L. Woolard, *J. Org. Chem.* **56**, 142 (1991).
7. S. Misaki, *J. Fluorine Chem.* **21**, 191 (1982); *Ibid.*, **17**, 159 (1981).
8. J. Ellis and W. K. R. Musgrave, *J. Chem. Soc.*, 3608 (1950).
9. M. M. Boudakian and G. A. Hyde, *J. Fluorine Chem.* **25**, 435 (1984).
10. R. Filler, *Isr. J. Chem.* **17**, 71 (1978).
11. A. Zweig and co-workers, *J. Org. Chem.* **45**, 3597 (1980).
12. S. Stavber and M. Zupan, *J. Org. Chem.* **50**, 3609 (1985).
13. M. J. Fifolt and co-workers, *J. Org. Chem.* **50**, 4576 (1985).
14. S. Rozen and co-workers, *J. Org. Chem.* **49**, 806 (1984); *Ibid.*, **46**, 4629 (1981).
15. D. Hebel and co-workers, *Tetrahedron Lett.* **31**, 619 (1990).
16. S. Singh and co-workers, *J. Am. Chem. Soc.* **109**, 7194 (1987).
17. E. Differding and H. Ofner, *SYNLETT*, 187 (Mar. 1991); *Chem. Eng. News*, 33 (Sept. 7, 1992).
18. T. Umemoto and co-workers, *J. Am. Chem. Soc.* **112**, 8563 (1990).
19. A. G. Gilicinski and co-workers, *J. Fluorine Chem.* **59**, 157 (1992).
20. R. E. Banks and co-workers, *J. Chem. Soc., Chem. Commun.*, (8), 595 (1992).
21. Ger. Pat. 600,706 (July 30, 1934), P. Osswald and O. Scherer (to I. G. Farbenind.); F. O. Robitschek and B. H. Wilcoxon, *FIAT Final Report*, No. 998, Mar. 31, 1947.
22. R. L. Ferm and C. A. VanderWerf, *J. Am. Chem. Soc.* **72**, 4809 (1950).
23. T. Fukuhara and co-workers, *Synth. Commun.* **17**, 685 (1987).
24. G. A. Olah and J. Welch, *J. Am. Chem. Soc.* **97**, 208 (1975).
25. U.S. Pat. 4,096,196 (June 20, 1978), M. M. Boudakian (to Olin).
26. U.S. Pat. 4,075,252 (Feb. 21, 1978), M. M. Boudakian (to Olin).
27. U.S. Pat. 4,912,268 (Mar. 27, 1990), M. H. Krackov and C. H. Ralston (to Du Pont).
28. D. T. Flood, *Org. Synth., Coll. Vol.* **II**, 295 (1943).
29. A. Roe, in R. Adams, ed., *Organic Reactions*, Vol. **5**, John Wiley & Sons, Inc., New York, 1949, Chapt. 4, p. 193.
30. H. Suschitzky, in M. Stacey, J. C. Taylor, and A. G. Sharpe, eds., *Advances in Fluorine Chemistry*, Vol. **4**, Butterworths, Washington, D.C., 1964, p. 1.
31. K. G. Rutherford and co-workers, *J. Org. Chem.* **26**, 5149 (1961).
32. M. P. Doyle and W. J. Bryker, *J. Org. Chem.* **44**, 1572 (1979).
33. U.S. Pat. 4,476,320 (Oct. 9, 1984), H. Diehl, H. Pelster, and H. Habetz (to Bayer).
34. D. J. Milner, *Synth. Commun.* **22**, 73 (1992).
35. L. Treschanke, Riedel-de Haën, personal communication, Feb. 5, 1992.
36. J. P. Regan, *Specialty Chemicals* **21**, 56 (Jan. 1986).
37. U.S. Pat. 2,705,730 (Apr. 5, 1955), J. D. Head (to Dow).
38. *Chem. Eng. News*, 65 (Apr. 24, 1961).
39. O. Wallach, *Ann. Chem.* **235**, 255 (1886).
40. O. Wallach and F. Heusler, *Ann. Chem.* **243**, 219 (1888).
41. U.S. Pat. 4,194,054 (Mar. 18, 1980), H. Förster and co-workers (to Bayer).
42. Ger. Pat. 3,142,856 (May 11, 1983), E. Klauke and K. Grohe (to Bayer).
43. T. J. Tewson and M. Welch, *J. Chem. Soc., Chem. Commun.*, 1149 (1979).
44. W. Prescott, *Chem. Ind. London*, 56 (1978); L. Dolby-Glover, *Chem. Ind. London*, 518 (1986).
45. Y. Kimura, *J. Synth. Org. Chem., Japan* **47**, 258 (1989).
46. G. C. Finger and co-workers, *J. Am. Chem. Soc.* **78**, 6034 (1956); *Chem. Ind. London*, 1328 (1962).
47. A. J. Beaumont and J. H. Clark, *J. Fluorine Chem.* **32**, 295 (1991).
48. Y. Uchibori and co-workers, *SYNLETT*, 345 (Apr. 1992).
49. N. Ishikawa and co-workers, *Chem. Lett.*, 761 (1981).
50. Y. Kimura and H. Suzuki, *Tetrahedron Lett.* **30**, 1271 (1989).
51. U.S. Pat. 4,069,262 (Jan. 17, 1978), R. A. Kunz (to Du Pont).
52. U.S. Pat. 4,642,399 (Feb. 10, 1987), C. R. White (to Mallinckrodt).

53. U.S. Pat. 4,287,374 (Sept. 1, 1981), R. A. North (to Boots).
54. C. Liotta and H. P. Harris, *J. Am. Chem. Soc.* **96**, 2250 (1974).
55. U.S. Pat. 4,642,398 (Feb. 10, 1987), G. L. Cantrell (to Mallinckrodt).
56. S. Kumai and co-workers, *Reports Res. Lab. Asahi Glass Co.* **39**, 317 (1989).
57. J. Deutsch and H.-J. Niclas, *Synth. Commun.* **21**, 205 (1991).
58. U.S. Pat. 4,429,365 (Oct. 21, 1980), H.-G. Oeser and co-workers (to BASF).
59. Y. Yoshida and Y. Kimura, *J. Fluorine Chem.* **44**, 291 (1989).
60. R. E. Banks and co-workers, *J. Fluorine Chem.* **46**, 529 (1990).
61. Y. Yoshida and co-workers, *J. Fluorine Chem.* **53**, 301 (1991).
62. N. C. O'Reilly and co-workers, *SYNLETT*, 609 (Oct. 1990).
63. Y. Yoshida and co-workers, *J. Fluorine Chem.* **53**, 335 (1991).
64. U.S. Pat. 4,937,396 (June 26, 1990), R. G. Pews and co-workers (to Dow).
65. U.S. Pat. 3,240,824 (Mar. 15, 1966), M. M. Boudakian and E. R. Shipkowski (to Olin).
66. *Chem. Eng. News* **29**, 2666 (1951).
67. D. G. Mooney, *Inst. Chem. Eng. Symp. Series* **124**, 381 (1991); A. T. Cates, *J. Hazard. Mater.* **32**, 1 (1992).
68. L. Bretherick, *Handbook of Reactive Chemical Hazards*, 4th ed., Butterworths, London, 1990.
69. G. Bartoli and co-workers, *J. Chem. Soc. Perkin Trans.* **1**, 2671 (1972).
70. F. Effenberger and W. Streicher, *Chem. Ber.* **124**, 157 (1991).
71. S. Kumai and co-workers, *Reports Res. Lab. Asahi Glass Co.* **35**, 153 (1985).
72. U.S. Pat. 4,568,781 (Feb. 4, 1986), F. Effenberger and W. Streicher (to BASF); H. Suzuki and co-workers, *Bull. Chem. Soc. Jpn.* **63**, 2010 (1990).
73. M. Stacey and J. C. Tatlow, in M. Stacey, C. Tatlow, and A. G. Sharpe, eds., *Advances in Fluorine Chemistry*, Vol. **1**, Butterworths, London, 1960, p. 166.
74. P. A. Coe and co-workers, *J. Chem. Soc. C.*, 1060 (1969).
75. R. D. Chambers and co-workers, *Tetrahedron* **19**, 891 (1963).
76. G. M. Brooks and co-workers, *J. Chem. Soc.*, 729 (1964).
77. U.S. Pat. 3,499,942 (Mar. 10, 1970), O. M. Nevedov and A. Ivashenko.
78. N. Ishikawa, *Senryo to Yakuhin* **26**(6), 106 (1981); *J. Synth. Org. Chem., Jpn.* **40**(2), 158 (1982).
79. N. V. Volchkov and co-workers, *Bull. Acad. Sci. USSR* **38**, 1782 (1989). (Engl. trans.).
80. U.S. Pat. 4,390,740 (June 28, 1983), I. Tabushi and co-workers (to Daikin Kogyo).
81. R. E. Ehrenkaufer and co-workers, *J. Org. Chem.* **47**, 2489 (1982).
82. G. A. Olah and P. Kreienbühl, *J. Org. Chem.* **32**, 1614 (1967).
83. K. O. Christe and A. E. Pavlath, *J. Org. Chem.* **31**, 559 (1966).
84. D. P. Ashton and co-workers, *J. Fluorine Chem.* **27**, 263 (1985); U.S. Pat. 4,745,235 (May 17, 1988), D. P. Ashton and co-workers (to ICI).
85. Fr. Demande Pat. 2,647,106 (Nov. 23, 1990), L. Gilbert and co-workers (to Rhône-Poulenc).
86. Eur. Pat. Appl. 427,603 (May 15, 1991), H. Garcia and co-workers (to Rhône-Poulenc).
87. G. G. Yakobson and co-workers, *Zh. Vses. Khim. Obshchestva im. D. I. Mendeleeva* **10**, 466 (1965).
88. M. Van Der Puy, *J. Org. Chem.* **53**, 4398 (1988); U.S. Pat. 5,081,275 (Jan. 14, 1992) (to AlliedSignal).
89. Y. Yazawa and co-workers, *Chem. Lett.*, 2213 (1989).
90. I. N. Rozhkov and co-workers, *Isv. Akad. Nauk SSSR Ser. Khim.*, 1130 (1972); *Russian Chem. Rev.* **45**, 615 (1976) (Engl. trans.).
91. Ger. Offen. 2,516,355 (Oct. 28, 1976), F. Beck (to BASF).
92. Jpn. Kokai Tokkyo Koho JP 63,111,192 (May 16, 1988), A. Shimizu and K. Yamatka (to Asahi Chemical Ind.); Jpn. Kokai Tokkyo Koho 62,127,488 (June 9, 1987), A. Shimizu and K. Yamatka (to Asahi Chemical Ind.).
93. J. H. H. Meurs and co-workers, *Angew. Chem. Int. Ed. Engl.* **28**, 927 (1989).
94. U.S. Pat. 2,884,458 (Apr. 28, 1959), D. A. Fidler (to Olin).
95. D. A. Fidler, J. S. Logan, and M. M. Boudakian, *J. Org. Chem.* **26**, 4014 (1961).
96. P. H. Scott and co-workers, *Tetrahedron Lett.*, 1153 (1970); U.S. Pat. 3,558,707 (Jan. 26, 1971), J. W. Churchill and E. H. Kober (to Olin).
97. Brit. Pat. Appl. 2,241,952 (Sept. 18, 1991), D. Levin and J. S. Moillet (to ICI).
98. Jpn. Kokai Tokkyo Koho 01,238,560 (Sept. 22, 1989), J. Negishi and T. Kawai (to Central Glass).

99. Eur. Pat. 248,746 (Apr. 25, 1990), M. Desbois (to Rhône-Poulenc).
100. U.S. Pat. 3,910,985 (Oct. 7, 1975), P. P. Montijn (to Shell Oil).
101. Span. ES 493,977 (Aug. 1, 1981), A. L. Porta (to Dr. Andreu S. A.).
102. A. I. Titov and A. N. Baryshnikova, *J. Gen. Chem. (USSR)* **23**, 346 (1953) (Engl. trans.).
103. U.S. Pat. 4,391,991 (July 5, 1983), P. F. Mundhenke and M. J. Fifolt (to Occidental Chemical).
104. PCT Int. Appl. WO 91 17,138 (Nov. 14, 1991), T. F. Braish (to Pfizer).
105. U.S. Pat. 4,367,350 (Jan. 4, 1983), U. Hiramatsu and co-workers (to Daikin Kogyo); U.S. Pat. 4,400,563 (Apr. 23, 1983), Y. Ohsaka and co-workers (to Daikin Kogyo).
106. G. A. Boswell and co-workers, *Organic Reactions* **21**, 1 (1974).
107. C.-L. Wang, *Organic Reactions* **34**, 319 (1985).
108. U.S. Pat. 3,976,691 (Aug. 24, 1976), W. J. Middleton (to Du Pont).
109. U.S. Pat. 4,533,777 (Aug. 6, 1985), A. Marhold and E. Klauke (to Bayer).
110. A. Marhold and E. Klauke, *J. Fluorine Chem.* **18**, 281 (1981).
111. V. C. R. McLaughlin and J. Thrower, *Tetrahedron* **25**, 5921 (1969).
112. Y. Kobayashi and I. Kumadaki, *Tetrahedron Lett.*, 4095 (1969); *Chem. Pharm. Bull.* **18**, 2334 (1970).
113. D. M. Wiemers and D. J. Burton, *J. Am. Chem. Soc.* **108**, 832 (1986).
114. J. H. Clark and co-workers, *J. Fluorine Chem.* **50**, 411 (1950).
115. J. M. Paratian and co-workers, *J. Chem. Soc., Chem. Commun.*, 53 (1992).
116. K. Matsui and co-workers, *Chem. Lett.*, 1719 (1981).
117. J. N. Freskos, *Synth. Commun.* **18**, 965 (1988).
118. B. R. Langlois and co-workers, *Tetrahedron Lett.* **32**, 7525 (1991).
119. J. G. MacNeil and D. J. Burton, *J. Fluorine Chem.* **55**, 225 (1991).
120. Q.-Y. Chen and co-workers, *J. Fluorine Chem.* **55**, 291 (1991).
121. H. Sawada and co-workers, *J. Fluorine Chem.* **46**, 423 (1990).
122. T. Umemoto and co-workers, *Chem. Lett.*, 1663 (1981).
123. W. A. Sheppard, *J. Am. Chem. Soc.* **87**, 2410 (1965).
124. A. F. Feiring, *J. Fluorine Chem.* **10**, 375 (1977); *J. Org. Chem.* **44**, 1252 (1979).
125. P. Martin, *Tetrahedron* **41**, 4057 (1985).
126. *Handbook of Aromatic Fluorine Compounds*, Olin Corp., Stamford, Conn., 1976.
127. D. V. Sweet, ed., *Registry of Toxic Effects of Chemical Substances-1985/1986 Edition*, Vols. **1**–**5**, DHHS (NIOSH) publication no. 87-114, Washington, D.C., 1987.
128. G. A. Olah and co-workers, *J. Chem. Soc.*, 1823 (1957).
129. P. A. Janssen and co-workers, *J. Med. Pharm. Chem.* **1**, 281 (1959).
130. H. C. Brown and G. Marino, *J. Am. Chem. Soc.* **84**, 1658 (1962).
131. P. A. Staniland, in G. Allen and J. C. Bevington, eds., *Comprehensive Polymer Science*, Vol. **5**, Pergamon Press, New York, 1989, Chapt. 29, p. 490.
132. P. M. Hergenrother and co-workers, *Polymer* **29**, 358 (1988).
133. P. M. Hergenrother and co-workers, *J. Polym. Sci. Part A: Polym. Chem.* **29**, 1483 (1991).
134. M. E. Neubert and D. L. Fishel, *Mol. Cryst. Liq. Cryst.* **53**, 101 (1979).
135. P. A. Worthington, in D. R. Baker and co-workers, eds., *Synthesis and Chemistry of Agrochemicals*, ACS Symposium Series no. 355. American Chemical Society, Washington, D.C. 1987, Chap. 27, p. 302.
136. U.S. Pat. 4,522,754 (June 11, 1985), B. Hilti and co-workers (to Ciba-Geigy).
137. R. E. Parker, in M. Stacey, J. C. Tatlow, and A. G. Sharpe, eds., *Advances in Fluorine Chemistry*, Vol. **3**, Butterworths, Washington, D.C., 1963, p. 63.
138. M. Bil, *J. Appl. Chem. Biotechnol.* **22**, 853 (1972); *Chem. Ind. London*, 656 (1971).
139. U.S. Pat. 3,959,377 (May 25, 1976) and U.S. Pat. 3,632,582 (Jan. 4, 1972), M. Bil (to Clairol).
140. Ger. Offen. 3,534,369 (Apr. 3, 1986), J. F. Grollier and co-workers (to Oreal).
141. F. Sanger, *Biochem. J.* **39**, 507 (1945).
142. S. E. Drewes and co-workers, *J. Chem. Soc., Perkin Trans.* **1**, 1283 (1975).
143. G. W. J. Fleet and R. Porter, *Nature*, 511 (1970).
144. K. J. Skinner, *Chem. Eng. News*, 23 (Aug. 18, 1975).
145. E. D. Bergmann and M. Bentov, *J. Org. Chem.* **26**, 1480 (1961).

146. R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.* **74**, 1110 (1952).
147. F. F. Micheel and co-workers, *Ann. Chem.* **581**, 238 (1953).
148. H. Zahn and K. H. Lebkücher, *Biochem. Z.* **334**, 133 (1961).
149. H. Zahn and H. Zuber, *Ber.* **86**, 172 (1953).
150. H. Zahn and J. Meinhoffer, *Makromol. Chem.* **26**, 126 (1958).
151. K. L. Kirk and L. A. Cohen, *J. Org. Chem.* **34**, 395 (1969).
152. Y. Watanabe and Y. Imai, *J. Chromatogr.* **239**, 723 (1982).
153. P. Marfey, *Carlsberg Res. Commun.* **49**, 591 (1984).
154. A. E. Katz and co-workers, *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **33**(3), 144 (1991).
155. K. Sturm and co-workers, *Chem. Ber.* **99**, 328 (1966).
156. U.S. Pats. 3,668,248 (June 6, 1972) and 3,419,552 (Dec. 31, 1968), C. W. Whitehead and J. J. Traverso (to Eli Lilly).
157. R. N. Johnson and co-workers, *J. Polym. Sci. Part A-1* **5**, 2375 (1967).
158. A. E. Feiring and co-workers, *J. Polym. Sci. Part A: Polym. Chem.* **28**, 2809 (1990).
159. U.S. Pat. 5,084,548 (Jan. 28, 1992), A. E. Feiring and S. D. Archer (to Du Pont).
160. U.S. Pat. 5,034,034 (July 23, 1991), E. S. Sanders and T. L. Parker (to Dow).
161. H. R. Kricheldorf and M. Bergahn, *Makromol. Chem., Rapid Commun.* **12**, 529 (1991).
162. M. M. Boudakian and co-workers, *J. Org. Chem.* **26**, 4641 (1961).
163. G. G. Yakobson and co-workers, *Dokl. Akad. Nauk SSSR* **141**, 1395 (1961).
164. S. H. Yu and E. C. Ashby, *J. Org. Chem.* **36**, 2123 (1971).
165. W. K. Moberg and co-workers, in Ref. 135, Chapt. 26, p. 288.
166. E. D. Morgan and C. F. Poole, *J. Chromatogr.* **104**, 351 (1975).
167. L. Bretherick, *Chem. Ind. London*, 1017 (1971).
168. A. J. Adduci, *Chemtech*, 575 (Sept. 1976).
169. M. Tsubouchi and co-workers, *Anal. Chem.* **57**, 783 (1985).
170. D. W. Ribbons and co-workers, *J. Fluorine Chem.* **37**, 299 (1987).
171. S. C. Taylor and co-workers, *Performance Chemicals*, 18 (Nov. 1986); *Specialty Chemicals* **8**(3), 236 (June 1988).
172. Eur. Pat. Appl. 253,438 (Jan. 20, 1988), J. A. Schofield and co-workers (to Shell Int. Research).
173. Ger. Offen. 3,520,316 (Dec. 11, 1986), E. Begemann and H. Schmand (to Riedel-de Haën).
174. U.S. Pat. 4,822,927 (Apr. 18, 1989), N. J. Stepaniuk and B. J. Lamb (to Mallinckrodt).
175. U.S. Pat. 4,812,572 (Mar. 14, 1989), M. S. Howarth and D. M. Tomkinson (to ICI).
176. U.S. Pat. 2,939,766 (June 7, 1960), J. W. Churchill (to Olin).
177. U.S. Pat. 5,032,371 (July 16, 1991), H. J. Buehler (to Mallinckrodt).
178. U.S. Pat. 2,563,796 (Aug. 7, 1951), (to Harshaw Chemical).
179. U.S. Pat. 3,160,623 (Dec. 8, 1964), L. G. Anello and C. Woolf (to Allied Chemical).
180. F. Seel, *Angew. Chem. Int. Ed. Engl.* **4**, 635 (1965).
181. Jpn. Kokai 74 81,330 (Aug. 6, 1974), S. Misaki and M. Okamoto (to Daikin Kogyo).
182. D. Hunter, *Chem. Week* **148**(27), 36 (July 24, 1991); *Ibid*, **146**(9), 41 (Mar. 1, 1989).
183. F. J. Weigert and W. A. Sheppard, *J. Org. Chem.* **25**, 4006 (1976).
184. R. Filler and S. M. Naqvi, in R. Filler and Y. Kobayashi, eds., *Biomedicinal Aspects of Fluorine Chemistry*, Kodansha Biomedical Press, Tokyo, 1982, Chapt. 1, p. 28.
185. P. H. Bolton and co-workers, *Biopolymers* **20**, 435 (1981).
186. H. J. Plach, *New LC Mixtures for STN and Active Matrix Displays Using New Terminally Fluorinated Compounds*, technical literature, E. Merck & Co., Darmstadt, Oct. 1990.
187. R. Neef, *The Merck Group Liquid Crystal Newsletter*, (7) (Feb. 1991), (8) (Sept. 1991), Darmstadt.
188. U.S. Pat. 5,077,160 (Dec. 31, 1991), K.-Y. Law and F. C. Bailey (to Xerox).
189. K.-Y. Law and F. C. Bailey, *J. Imaging Sci.* **31**, 172 (1987).
190. K.-Y. Law and co-workers, *Dyes and Pigments* **9**, 187 (1988).
191. P. M. Kazmeier and co-workers, *J. Imaging Sci.* **32**, 1 (1988).
192. H. Hopff, *Chimia* **15**, 193 (1961).
193. J. T. Minor and C. A. VanderWerf, *J. Org. Chem.* **17**, 1425 (1952).
194. Jpn. Kokai Tokkyo Koho JP 03,232,828 (Oct. 16, 1991), K. Momota and T. Yonezawa (to Morita Kagaku).
195. U.S. Pat. 5,055,220 (Oct. 8, 1991), M. Uchida and co-workers (to Chisso).

196. M. Hird and co-workers, *Liquid Crystals* **11**, 531 (1992).
197. Jpn. Kokai Tokkyo Koho JP 61 63,627 (Apr. 1, 1986), N. Yoneda and co-workers (to Mitsubishi Chemical).
198. G. Schiemann and R. Pillarsky, *Chem. Ber.* **62**, 3035 (1929).
199. G. Furin and co-workers, in I. L. Knunyants and G. G. Yakobson, eds., *Syntheses of Fluoroorganic Compounds*, Springer-Verlag, Berlin, 1985, Chapt. 2, p. 109.
200. Jpn. Kokai Tokkyo Koho JP 03 34,944 (Feb. 14, 1991), T. Mogi (to Tokemu Product K.K.).
201. G. D. Hartman and S. E. Biffar, *J. Org. Chem.* **42**, 1468 (1977).
202. Brit. Pat. 1,514,082 (June 14, 1978), G. Fuller (to ISC).
203. Brit. Pat. Appl. 2,058,067 (Apr. 8, 1988), D. Wotton (to ISC).
204. R. H. Shiley, D. R. Dickerson and G. C. Finger, *J. Fluorine Chem.* **2**, 19 (1972/73).
205. A. M. Roe, R. A. Burton, and D. R. Reavill, *J. Chem. Soc., Chem. Commun.*, 582 (1965).
206. W. J. Feast and R. Stephens, *J. Chem. Soc.*, 3502 (1965).
207. I. Hayakawa and co-workers, *Chem. Pharm. Bull.* **32**, 4907 (1984).
208. U.S. Pat. 4,528,287 (July 9, 1985), Y. Itoh and co-workers (to Hokuriku Pharmaceutical).
209. G. C. Finger and R. E. Oesterling, *J. Am. Chem. Soc.* **78**, 2593 (1956).
210. T. F. Braish and D. E. Fox, *Org. Prep. Proced. Int.* **23**, 655 (1991).
211. G. C. Finger and co-workers, *J. Am. Chem. Soc.* **73**, 145 (1951).
212. J. P. Sanchez and co-workers, *J. Med. Chem.* **31**, 983 (1988); *Ibid.* **35**, 361 (1992).
213. D. T. W. Chu and co-workers, *Can. J. Chem.* **70**, 1323 (1992).
214. U.S. Pat. 5,021,605 (June 4, 1991), H. Kobayashi and M. Shimizu (to SDS Biotech).
215. U.S. Pat. 4,885,386 (Dec. 5, 1989), J. N. Wemple and co-workers (to Warner-Lambert).
216. G. C. Finger and co-workers, *J. Am. Chem. Soc.* **73**, 153 (1951).
217. Eur. Pat. Appl. 460,639 (Dec. 11, 1991), Y. Kobayashi and co-workers (to SDS Biotech).
218. T. Ishizaki and co-workers, *Nippon Kagaku Kaishi*, 2054 (1985).
219. U.S. Pat. 4,782,180 (Nov. 1, 1988), J. N. Wemple and co-workers (to Warner-Lambert).
220. U.S. Pat. 5,047,553 (Sept. 10, 1991), D. M. Novak and H. C. Lin (to Occidental Chemical).
221. D. G. Holland and co-workers, *J. Org. Chem.* **29**, 3042 (1964).
222. U.S. Pat. 4,952,695 (Aug. 28, 1990), K. Grohe and co-workers (to Bayer).
223. D. T. W. Chu and co-workers, *J. Med. Chem.* **30**, 504 (1987).
224. H. Egawa and co-workers, *Chem. Pharm. Bull.* **34**, 4098 (1986).
225. S. K. Ray, *Adv. Energy Convers.* **6**, 89 (1966).
226. G. Fuller, *J. Chem. Soc.*, 6264 (1965).
227. Brit. Pat. 996,498 (June 30, 1965), G. Fuller (to ISC).
228. J. M. Birchall and co-workers, *J. Chem. Soc.*, 4966 (1962).
229. P. L. Coe and co-workers, *J. Chem. Soc. C*, 2323 (1966).
230. M. M. Murza and co-workers, *Zh. Org. Khim.* **13**, 1046 (1977).
231. I. Kisfaludy and co-workers, *Tetrahedron Lett.*, 1785 (1974).
232. G. H. Kalb and co-workers, *Appl. Polym. Symposium*, (22), 127 (1973).
233. G. H. Kalb and co-workers, in N. A. J. Platzer ed., *Polymerization Reactions and New Polymers*, Advances in Chemistry Series no. 129, American Chemical Society, Washington, D.C., 1973, Chapt. 2, p. 13.
234. F. K. Kawahara, *Anal. Chem.* **40**, 2073 (1968).
235. R. J. Harper and co-workers, *J. Org. Chem.* **29**, 3042 (1964).
236. E. Kinsella and A. G. Massey, *Chem. Ind. London*, 1017 (1971).
237. S. C. Cohen and A. G. Massey, in J. C. Tatlow, R. D. Peacock, and H. H. Hyman, eds., *Advances in Fluorine Chemistry*, Vol. **6**, CRC Press, Cleveland, Ohio, 1970, p. 83.
238. J. W. Eichelberger and co-workers, *Anal. Chem.* **47**, 995 (1975).
239. T. Nakamura and O. Kaieda, *J. Synth. Org. Chem., Jpn.* **47**, 20 (1989).
240. J. Wallace and co-workers, *Clin. Chem.* **25**, 252 (1979); *Ibid* **24**, 895 (1978).
241. J. Wallace and co-workers, *Anal. Chem.* **49**, 903 (1977).
242. J. C. Lhuguenot and B. F. Baume, *J. Chromatogr. Sci.* **12**, 411 (1974).
243. K. T. Koshy and co-workers, *J. Chromatogr. Sci.* **13**, 97 (1975).
244. T. Nambara and co-workers, *J. Chromatogr.* **114**, 81 (1975).

245. U.S. Pat. 3,946,063 (May 23, 1976), J. Vessman and co-workers (to Pierce Chemical).
246. K. Blau and G. S. King, eds., *Handbook of Derivatives for Chromatography*, Heyden, London, 1977.
247. R. Filler, *Fluorine Chem. Rev.* **8**, 1 (1977).
248. L. A. Wall, ed., *Fluoropolymers*, Vol. **25**, Wiley-Interscience, New York, 1972.
249. G. W. Holbrook, L. A. Loree, and O. R. Pierce, *J. Org. Chem.* **31**, 1259 (1966).
250. N. N. Vorozhtsov, Jr. and co-workers, *Isv. Akad. Nauk SSSR, Ser. Khim.* (8), 1524 (1963).
251. Y. Désirant, *Bull. Acad. Sci. Roy. Belg.* **41**, 759 (1955).
252. J. M. Birchall and R. N. Haszeldine, *J. Chem. Soc.*, 13 (1959).
253. L. A. Wall and co-workers, *J. Research NBS* **65A**, 239 (1961).
254. R. A. Falk, *Sperry Eng. Rev.* **16**(3), 24 (Fall 1963).
255. U.S. Pat. 3,158,657 (Nov. 24, 1964), F. R. Callihan and C. L. Quateta (to Sperry Rand).
256. L. S. Kobrina, *Fluorine Chem. Rev.* **7**, 1 (1974).
257. U.S. Pat. 5,087,764 (Feb. 11, 1992), V. Reiffenrath and J. Krause (to E. Merck GmbH).
258. U.S. Pat. 5,064,567 (Nov. 12, 1991), F. Funada and co-workers (to Sharp and E. Merck GmbH).
259. A. Villiger and F. Leenhouts, *Mol. Cryst. Liq. Cryst.* **209**, 297 (1991).
260. Jpn. Kokai Tokkyo Koho JP 03,197,438 (Aug. 28, 1991), N. Satake and co-workers (to Kanto Chemical).
261. Brit. Pat. Appl. 2,232,416 (Dec. 12, 1990), D. Coates and co-workers (to U.K. Secretary of State for Defence).
262. Jpn. Kokai Tokkyo Koho JP 03,176,445 (July 31, 1991), T. Kuriyama and co-workers (to Dainippon).
263. U.S. Pat. 5,032,314 (July 16, 1991), M. Ushioda and co-workers (to Chisso).
264. Jpn. Kokai Tokkyo Koho JP 04 29,951 (Jan. 31, 1992), T. Watanabe and M. Sato (to Sanyo Chemical).
265. M. Hird and co-workers, *Liquid Crystals* **11**, 531 (1992).
266. U.S. Pat. 5,061,400 (Oct. 29, 1991), T. Obikawa (to Seiko Epson).
267. G. Schiemann and E. Bolstead, *Chem. Ber.* **61B**, 1403 (1928).
268. J. Hannah and co-workers, *J. Med. Chem.* **21**, 1093 (1978).
269. U.S. Pat. 4,443,631 (Apr. 13, 1984), A. G. Padilla (to Upjohn).
270. W. J. Pummer and L. A. Wall, *J. Chem. Eng. Data* **6**, 76 (1961).
271. M. W. Buxton and co-workers, *J. Fluorine Chem.* **2**, 387 (1972/73).
272. F. Mercer and co-workers, *J. Polym. Sci., Part A: Polym. Chem.* **30**, 1767 (1992); U.S. Pat. 5,114,780 (May 19, 1992), F. Mercer and co-workers (to Raychem).
273. M. S. Newman, in P. O. P. Ts'o and J. D. DiPaolo, eds., *Chemical Carcinogenesis*, Marcel Dekker, Inc., New York, 1974, p. 177.
274. D. R. MacKenzie and co-workers, *J. Phys. Chem.* **69**, 2526 (1965).
275. E. Boger and co-workers, *J. Fluorine Chem.* **8**, 513 (1976).
276. O. Lerman and co-workers, *J. Org. Chem.* **49**, 806 (1984).
277. S. Stavber and M. Zupan, *J. Fluorine Chem.* **17**, 597 (1981).
278. I. N. Rozhkov and co-workers, *Dokl. Akad. Nauk SSSR, Chem. Sect.* **193**, 618 (1970) (Engl. trans.).
279. R. F. O'Malley and co-workers, *J. Org. Chem.* **46**, 2816 (1981); *J. Electrochem. Soc.* **130**, 2170 (1983).
280. U.S. Pat. 3,707,843 (Jan. 2, 1973), R. C. Connor and L. L. Ferstandig (to Halocarbon Products).
281. U.S. Pat. 3,753,345 (Aug. 21, 1973), F. H. Cassidy and R. Garcia (to Aerojet-General).
282. E. Kühle and E. Klauke, *Angew. Chem. Int. Ed. Engl.* **16**, 735 (1977).
283. R. Filler and H. Novar, *Chem. Ind. London*, 1273 (1960).
284. R. G. Jones, *J. Am. Chem. Soc.* **69**, 2346 (1947).
285. V. C. R. McLoughlin and J. Thrower, *Chem. Ind. London*, 1557 (1964).
286. R. Grinter and co-workers, *Tetrahedron Lett.*, 3845 (1968).
287. R. Wächter, *Angew. Chem.* **67**, 305 (1955).
288. F. Swarts, *Bull. Sci. Acad. Roy. Belg.*, 399 (1920).
289. Y. Kobayashi and I. Kumadaki, *Acc. Chem. Res.* **11**, 197 (1978).
290. N. P. Buu-Hoi and co-workers, *Compt. Rend.* **257** (21), 3182 (1963).
291. *Product List No. 4*, Marshallton Research Labs, West Chester, Pa., Jan. 1973, p. 27.
292. L. Bretherick, *Chem. Ind. London*, 1017 (1971).
293. I. C. Appleby, *Chem. Ind. London*, 120 (1971).
294. E. C. Ashby and D. M. Al-Fekri, *J. Organometallic Chem.* **390**, 275 (1990).

295. U.S. Pat. 3,234,292 (Feb. 8, 1966), S. Robota and E. A. Belmore (to Hooker Chemical).
296. R. J. Albers and E. C. Kooyman, *Rec. Trav. Chim.* **83**, 930 (1964).
297. A. A. Ushakov and co-workers, *Zh. Org. Khim.* **12**, 158 (1963).
298. K. Inukai and T. Ueda, *Kogyo Kagaku Zasshi* **64**, 2156 (1961).
299. Jpn. Kokai 75 76,029 (June 21, 1975), S. Misaki and co-workers (to Daikin Kogyo).
300. U.S. Pat. 4,401,623 (Aug. 30, 1983), T. Giacobbe and G. Tsien (to Rhône-Poulenc).
301. E. T. McBee and co-workers, *J. Am. Chem. Soc.* **72**, 1651 (1950).
302. U.S. Pat. 4,008,278 (Feb. 15, 1977), M. M. Boudakian (to Olin).
303. Ger. Pat. 1,568,938 (Dec. 12, 1974), H. Treiber (to Knoll).
304. U.S. Pat. 4,144,265 (Mar. 13, 1979), W. Dowd and T. H. Fisher (to Dow).
305. U.S. Pat. 4,966,988 (Oct. 30, 1990), W. I. Schinski and P. Denisevich (to Chevron).
306. C. E. Ward and co-workers, in Ref. 135, Chapt. 6, p. 65.
307. A. L. Henne and M. S. Newman, *J. Am. Chem. Soc.* **60**, 1697 (1938).
308. W. Schwertfeger and G. Siegemund, *J. Fluorine Chem.* **36**, 237 (1987).
309. U.S. Pat. 4,978,798 (Dec. 18, 1990), J. S. Stults (to Occidental Chemical).
310. C. Saboureau and co-workers, *J. Chem. Soc., Chem. Commun.*, 1138 (1989).
311. R. Filler, in Ref. 237, p. 1.
312. *Benzotrifluoride*, data sheet no. 778-D, Hooker Chemical Corp., Niagara Falls, N.Y., 1969.
313. F. Swarts, *Bull. Acad. Roy. Belg. Cl. Sci.* **35**, 375 (1898).
314. A. K. Barbour, L. J. Belf, and M. W. Buxton, in M. Stacey, J. C. Tatlow, and A. G. Sharpe, eds., *Advances in Fluorine Chemistry*, Vol. **3**, Butterworths, London, 1963, p. 181.
315. J. H. Brown and co-workers, *J. Chem. Soc. Suppl. Issue* **1**, S95 (1949).
316. U.S. Pat. 3,966,832 (June 26, 1978), R. Lademann and co-workers (to Hoechst).
317. Ger. Pat. 1,618,390 (Sept. 28, 1972), O. Scherer and co-workers (to Hoechst).
318. U.S. Pat. 4,183,873 (Jan. 15, 1980), Y. Baxamusa and S. Robota (to Hooker Chemical).
319. U.S. Pat. 4,130,594 (Dec. 19, 1978) and U.S. Pat. 4,129,602 (Dec. 12, 1978), L. Sendlak (to Hooker Chemical).
320. U.S. Pat. 4,462,937 (July 31, 1984), A. Ramanadin and L. Seigneurin (to Rhône-Poulenc).
321. U.S. Pat 3,859,372 (Jan. 7, 1975), S. Robota (to Hooker Chemical).
322. Y. A. Fialkov and L. M. Yagupolski, in Ref. 199, Chapt. 3, p. 233.
323. *para-Chlorobenzotrifluoride (OXSOL 100)*, data sheet no. 784 588, MSDS No. M29358, Occidental Chemical Co., Niagara Falls, N.Y., Dec. 26, 1991.
324. *3,4-Dichlorobenzotrifluoride (OXSOL 1000)*, data sheet no. 343, 588, MSDS No. M29478, Occidental Chemical Co., Niagara Falls, N.Y., Jan. 16, 1992.
325. U.S. Pat. 4,110,405 (Aug. 29, 1978), M. Bornengo (to Montedison).
326. Eur. Pat. Appl. 490,115 (June 17, 1992) and Eur. Pat. Appl. 484,767 (May 13, 1992), R. Krishnamurti and co-workers (to Occidental Chemical).
327. A. Pozdeeva, *Zh. Prikl. Khim. (Leningrad)* **52**, 1119 (1979).
328. G. A. Mandrov and co-workers, *Khim. Prom-st., Ser.: Metody Anal. Kontrolya Kach. Prod. Khim. Prom-sti.* (8), 10 (1981).
329. B. W. Lawrence and co-workers, *Manuf. Chem. Aerosol News* **41**, 37 (Jan. 1970).
330. *3-(Trifluoromethyl)aniline, BUA Substance Report 44 (Sept. 1989)*, Advisory Board for Environmental Relevant Waste of the German Chemical Society, VCH Publishers, Weinheim, Germany, 1990, 58 pp.
331. U.S. Pat. 4,582,935 (Apr. 15, 1986), M. M. Boudakian (to Olin).
332. M. M. Boudakian, *J. Fluorine Chem.* **36**, 283 (1987).
333. L. M. Yagupolski and co-workers, *Russian Chem. Rev.* **52**, 993 (1983) (Engl. trans.).
334. N. Ishikawa, *Senryo to Yakuhin* **28**, 52 (1983).
335. G. Wulfram, in R. E. Banks, ed., *Organofluorine Chemicals and Their Industrial Applications*, E. Horwood, Chichester, U.K., 1979, Chapt. 10, p. 208.
336. U.S. Pat. 5,030,252 (July 9, 1991), E. Sanders and T. L. Parker (to Dow).
337. U.S. Pat. 5,082,921 (Jan. 21, 1992), T. L. Parker (to Dow).
338. U.S. Pat. 4,876,329 (Oct. 24, 1989), W. L. Chiang and co-workers (to Amoco).
339. U.S. Pat. 5,021,540 (June 4, 1991), A. Leone-Bay and co-workers (to American Cyanamid).

340. F. M. Houlihan and co-workers, *Chem. Mater.* **3**, 462 (1991).
341. S. Misaki and co-workers, *Mol. Cryst. Liq. Cryst.* **66**, 443 (1981).
342. Jpn. Kokai Tokkyo Koho JP 59,16750 (Sept. 21, 1984) (to Chisso).
343. Jpn. Kokai Tokkyo Koho JP 03,200,737 (Sept. 2, 1991), S. Takehara and co-workers (to Dainippon).
344. A. C. Griffin and N. W. Buckley, *Mol. Cryst. Liq. Cryst.* **41**, 141 (1978).
345. H. Kobayashi and co-workers, *Chem. Lett.*, 1185 (1982).
346. G. E. Pacey and co-workers, *Analyst* **106**, 636 (1981).
347. U.S. Pat. 3,947,257 (Mar. 30, 1976), R. S. Johannsen and W. M. Moyer (to Raychem).
348. W. A. Sheppard, *J. Org. Chem.* **29**, 1 (1964).
349. F. E. Herkes, *J. Fluorine Chem.* **9**, 113 (1977).
350. G. A. Olah and co-workers, *J. Am. Chem. Soc.* **109**, 3708 (1987).
351. B. Langlois and M. Desbois, *Ann. Chim. Fr.*, 729 (1984).
352. Brit. Pat. 765,527 (Jan. 9, 1957) (to Hoechst).
353. U.S. Pat. 4,620,040 (Oct. 28, 1986), D. J. Alsop (to Occidental Chemical).
354. L. M. Yagupolski, *Dokl. Akad. Nauk (SSSR)* **105**, 100 (1955).
355. A. E. Feiring, *J. Org. Chem.* **44**, 2907 (1979).
356. F. Mathey and J. Bensoam, *Tetrahedron Lett.*, 2253 (1973).
357. L. M. Yagupolski and V. V. Orda, *Zh. Obsch. Khim.* **34**, 1979 (1964).
358. R. P. J. Braden and E. Klauke, *Pesticide Sci.* **17**, 418 (1986).
359. L. M. Yagupolski and co-workers, *Synthesis*, 721 (1975).
360. D. C. Remy and co-workers, *J. Org. Chem.* **41**, 1644 (1976).
361. T. G. Miller and J. W. Thanasi, *J. Org. Chem.* **25**, 2009 (1960).
362. B. R. Langlois, *J. Fluorine Chem.* **41**, 247 (1988).
363. D. C. England and co-workers, *J. Am. Chem. Soc.* **82**, 5116 (1960).
364. J. P. Idoux and co-workers, *J. Org. Chem.* **48**, 3771 (1983).
365. J. T. Gupton and co-workers, *Synth. Commun.* **15**, 431 (1985).
366. J. P. Idoux and co-workers, *J. Org. Chem.* **50**, 1876 (1985).
367. E. H. Banitt and co-workers, *J. Med. Chem.* **18**, 1130 (1975); *Ibid.* **20**, 821 (1977).
368. U.S. Pat. 5,082,587 (Jan. 21, 1992), E. P. Janulis (to 3M Co.).
369. World Pat. 91/00897 (Jan. 24, 1991). A. Wächtler and co-workers (to E. Merck GmbH).
370. N. Yoneda and co-workers, *J. Fluorine Chem.* **38**, 435 (1988).
371. M. M. Boudakian, *J. Fluorine Chem.* **18**, 497 (1981).
372. U.S. Pat. 2,447,717 (Aug. 24, 1948), J. H. Simons (to Minnesota Mining and Manufacturing).
373. H. Meinert, *Z. Chem.* **5**, 64 (1965).
374. M. Van der Puy, *Tetrahedron Lett.* **28**, 255 (1987).
375. U.S. Pat. 4,786,733 (Nov. 22, 1988), M. Van der Puy and R. E. Eibeck (to Allied-Signal).
376. S. P. Anand and R. Filler, *J. Fluorine Chem.* **7**, 179 (1976).
377. S. Stavber and M. Zupan, *Tetrahedron Lett.* **31**, 775 (1990).
378. T. Umemoto and G. Tomizawa, *J. Org. Chem.* **54**, 1726 (1989).
379. G. C. Finger and co-workers, *J. Org. Chem.* **28**, 1666 (1963).
380. M. M. Boudakian, *J. Heterocyclic Chem.* **4**, 381 (1967); U.S. Pat. 3,296,269 (Jan. 3, 1967), M. M. Boudakian (to Olin).
381. Jpn. Kokai Tokkyo Koho JP 04,124,176 (Apr. 24, 1992), T. Fukuhara and co-workers (to Tohkem Products).
382. H. C. Brown and D. McDaniel, *J. Am. Chem. Soc.* **77**, 3752 (1955).
383. L. Bradlow and C. VanderWerf, *J. Org. Chem.* **14**, 509 (1949).
384. G. Bressan and co-workers, *J. Chem. Soc. B.*, 225 (1971).
385. U.S. Pats. 3,873,701 (Mar. 25, 1975), and 3,816,406 (June 11, 1974), A. F. Hirsch (to Ortho Pharmaceuticals).
386. T. Mukaiyama, *Angew. Chem. Int. Ed. Engl.* **18**, 707 (1979).
387. J. Hannah and co-workers, *J. Med. Chem.* **25**, 457 (1982).
388. T. Güngör, *J. Organometallic Chem.* **215**, 139 (1981).
389. F. Marsais and co-workers, *J. Org. Chem.* **57**, 565 (1992).
390. R. D. Beaty and W. K. R. Musgrave, *J. Chem. Soc.*, 875 (1952).
391. A. Roe and C. Hawkins, *J. Am. Chem. Soc.* **69**, 2443 (1947).

392. *Chem. Eng. News*, 44 (Oct. 16, 1967); *Ibid.*, 8 (Dec. 8, 1967).
393. Span. Pat. ES 548,693 (May 16, 1986), J. C. Verde.
394. T. Miyamoto and co-workers, *Chem. Pharm. Bull.* **35**, 2280 (1987).
395. R. G. Pews and Z. Lysenko, *J. Org. Chem.* **50**, 5115 (1985).
396. T. Talik and Z. Talik, *Rocz. Chem.* **40**, 1187 (1966).
397. *Ibid.*, **38**, 785 (1964).
398. U.S. Pat. 3,637,714 (Jan. 25, 1972), L. A. F. Carlsson and co-workers (to Aktiebolaget Astra).
399. W. S. Saari and co-workers, *J. Med. Chem.* **26**, 1696 (1983).
400. U.S. Pat. 3,703,521 (Nov. 21, 1972), M. M. Boudakian (to Olin).
401. P. B. Desai, *J. Chem. Soc. Perkin Trans.* **1**, 1866 (1973).
402. U.S. Pats. 4,283,397 (Aug. 11, 1981), 4,255,424 (Mar. 10, 1981), 4,241,062 (Dec. 23, 1980), 4,263,306 (Apr. 21, 1981), and 4,282,219 (Aug. 4, 1981), J. Hannah (to Merck).
403. Ger. Offen. 2,128,540 (Dec. 16, 1971), A. Nicolson (to ICI).
404. Ger. Offen. 2,425,239 (May 24, 1973), D. W. R. Headford and co-workers (to ICI).
405. U.S. Pat. 3,798,228 (Mar. 19, 1974), M. M. Boudakian (to Olin).
406. J. Hamer and co-workers, *Rec. Trav. Chim.* **81**, 1059 (1962).
407. U.S. Pat. 4,071,521 (Jan. 31, 1978), T. G. Muench (to Dow).
408. U.S. Pat. 4,031,100 (June 21, 1977), T. L. Giacobbe (to Dow).
409. M. M. Boudakian, *J. Heterocyclic Chem.* **5**, 683 (1968).
410. U.S. Pat. 4,320,122 (Mar. 16, 1982), H. Theobold and co-workers (to BASF).
411. U.S. Pat. 3,810,902 (May 14, 1974), R. H. Rigterink (to Dow).
412. U.S. Pat. 4,115,557 (Sept. 19, 1978), C. E. Pawloski (to Dow).
413. H. R. Kricheldorf and co-workers, *Makromol. Chem.* **189**, 2255 (1988); *Ibid.* **191**, 2027 (1990).
414. F. Mutterer and C. D. Weis, *Helv. Chim. Acta* **59**, 229 (1976).
415. E. Differding and co-workers, *Bull. Soc. Chim. Belg.* **99**, 647 (1990).
416. R. D. Chambers and co-workers, *J. Chem. Soc.*, 5045 (1965).
417. U.S. Pat. 4,746,744 (May 24, 1988), C. A. Wilson and A. Fung (to Dow).
418. R. E. Banks and co-workers, *J. Chem. Soc.*, 594 (1965).
419. *Ibid.*, 575 (1965).
420. *Ibid.*, 1740 (1961).
421. J. A. Burdon and co-workers, *Nature* **196**, 231 (1960).
422. R. D. Chambers and co-workers, *J. Chem. Soc.*, 3573 (1964).
423. G. G. Yakobson and co-workers, *Fluorine Chem. Rev.* **7**, 115 (1974).
424. U.S. Pat. 3,850,943 (Nov. 26, 1974), R. D. Bowden and co-workers (to ICI).
425. U.S. Pat. 4,063,926 (Dec. 20, 1977), C. D. S. Tomlin and co-workers (to ICI).
426. R. D. Chambers and co-workers, *J. Chem. Soc. C*, 2221 (1968); *J. Chem. Soc., Chem. Commun.*, 384 (1966).
427. L. A. Mitscher and co-workers, *Chemtech*, 50 (Jan. 1991); *Ibid.*, 249 (Apr. 1991).
428. M. Jarman and R. McCague, *J. Chem. Soc., Chem. Commun.*, 125 (1984).
429. T. Miyamoto and co-workers, *J. Heterocyclic Chem.* **24**, 1333 (1987).
430. D. T. W. Chu and co-workers, *J. Med. Chem.* **29**, 2363 (1986).
431. J. Matsumoto and co-workers, *J. Heterocyclic Chem.* **21**, 673 (1984).
432. E. T. McBee and co-workers, *Ind. Eng. Chem.* **39**, 389 (1947).
433. U.S. Pat. 2,516,402 (July 25, 1950), E. T. McBee and E. M. Hodnett (to Purdue Research Foundation).
434. M. S. Raasch, *J. Org. Chem.* **27**, 1406 (1962).
435. I. D. Shustov and co-workers, *Zh. Obshch. Khim.* **53**, 103 (1983).
436. L. F. Lee and co-workers, *J. Org. Chem.* **55**, 2872 (1990).
437. L. F. Lee and co-workers, in D. R. Baker, J. G. Fenyes, and W. K. Moberg, eds., *Synthesis and Chemistry of Agrochemicals, II*. ACS Symposium Series No. 443, American Chemical Society, Washington, D.C., 1991, Chapt. 16, p. 195.
438. Y. Kobayashi and I. Kumadaki, *Chem. Pharm. Bull.* **17**, 510 (1969).
439. Y. Kobayashi and E. Chinen, *Chem. Pharm. Bull.* **17**, 510 (1967).
440. U.S. Pat. 4,259,496 (Mar. 31, 1981), G. Whittaker (to ICI).

441. U.S. Pat. 4,324,627 (Apr. 13, 1982), D. Cartwright (to ICI).
442. U.S. Pat. 4,266,064 (May 5, 1981), (to Ishihara).
443. U.S. Pats. 4,417,055 (Nov. 22, 1983), and 4,288,599 (Sept. 8, 1981), R. Nishiyama and co-workers (to Ishihara).
444. R. D. Chambers and co-workers, *J. Chem. Soc. C*, 2328 (1966).
445. Y. Kobayashi and co-workers, *Chem. Pharm. Bull.* **17**, 2335 (1969).
446. H. Gilman and D. Blume, *J. Am. Chem. Soc.* **65**, 2467 (1943).
447. E. Pouterman and A. Girardet, *Helv. Chim. Acta* **30**, 107 (1947).
448. C. J. Ohnmacht and co-workers, *J. Med. Chem.* **14**, 926 (1971).
449. H. Vergin and R. Metz, *Drugs of Today* **27**(3), 177 (1991).
450. *Chem. Mktg. Rep.*, 5 (Dec. 15, 1992).
451. R. Duschinsky and co-workers, *J. Am. Chem. Soc.* **79**, 4559 (1957).
452. U.S. Pat. 3,682,917 (Aug. 8, 1972), I. L. Knunyants and co-workers.
453. U.S. Pat. 3,846,429 (Nov. 5, 1974), S. A. Giller and co-workers.
454. U.S. Pats. 3,954,758 (May 4, 1976), and 4,113,949 (Sept. 12, 1978), P. D. Schuman and co-workers (to PCR).
455. U.S. Pat. 4,082,752 (Apr. 4, 1978), T. Takahara and S. Misaki (to Daikin Kogyo).
456. F. Winston, *PCR Research Chemicals Catalog, 1990–91*. Gainesville, Fla., p. 174.
457. E. Klauke and co-workers, *J. Fluorine Chem.* **21**, 495 (1982).
458. U.S. Pat. 3,314,955 (Apr. 18, 1967), M. M. Boudakian and C. W. Kaufman (to Olin).
459. U.S. Pat. 3,280,124 (Oct. 18, 1966), M. M. Boudakian and co-workers (to Olin).
460. R. G. Pews and W. E. Puckett, *J. Fluorine Chem.* **42**, 179 (1989).
461. H. Schroeder, *J. Am. Chem. Soc.* **82**, 4115 (1960).
462. H. Schroeder and co-workers, *J. Org. Chem.* **27**, 2580 (1962).
463. R. E. Banks and co-workers, *J. Chem. Soc. C*, 1822 (1967).
464. B. Baasner and E. Klauke, *J. Fluorine Chem.* **45**, 417 (1989).
465. D. R. Hildebrand, *Chemtech*, 224 (Apr. 1978).
466. W. Harms, in Ref. 335, Chapt. 9, p. 188.
467. U.S. Pat. 3,694,444 (Sept. 26, 1972), E. Klauke and H.-S. Bien (to Bayer); Brit. Pat. 1,273,914 (June 12, 1970), H.-U. Alles and co-workers (to Bayer).
468. Can. Pat. 844,625 (June 16, 1970), E. Klauke and H.-S. Bien (to Bayer).
469. Brit. Pat. 873,251 (July 19, 1961), A. Dorlars (to Bayer).
470. Ger. Offen. 2,729,762 (Jan. 18, 1979), F. Kysela and co-workers (to Bayer).
471. U.S. Pat. 4,332,939 (June 1, 1982), G. Seifert and S. Stäubli (to Ciba-Geigy).
472. C. W. Tullock and D. D. Coffman, *J. Org. Chem.* **25**, 2016 (1960).
473. U.S. Pat. 4,329,458 (May 11, 1982), E. Klauke and co-workers (to Bayer).
474. K. Kuriha and co-workers, *Biochem. Biophys. Acta* **384**, 127 (1975).
475. U.S. Pat. 2,975,179 (Mar. 14, 1961), A. Dorlars (to Bayer).
476. G. A. Olah and co-workers, *Synthesis*, 487 (1973).
477. L. A. Carpino and co-workers, *J. Am. Chem. Soc.* **112**, 9651 (1990); *J. Org. Chem.* **56**, 2611 (1991).
478. W. L. Reilly and H. C. Brown, *J. Org. Chem.* **22**, 698 (1967).
479. E. T. McBee and co-workers, *Ind. Eng. Chem.* **39**, 391 (1947).
480. S. Smith, in R. E. Banks, ed., *Preparation, Properties and Industrial Applications of Organofluorine Compounds*, E. Horwood, Chichester, U.K., 1982, Chapt. 8, p. 234.
481. J. A. Young, in Ref. 248, Chapt. 9.
482. K. Tanaka, *J. Synth. Org. Chem., Japan* **48**, 16 (1990).
483. R. D. Chambers and C. R. Sargent, in A. R. Katritzky and A. J. Boulton, eds., *Advances in Heterocyclic Chemistry*, Academic Press, Inc., New York, 1981, Vol. **28**, p. 1.

General References

484. A. E. Pavlath and A. L. Leffler, *Aromatic Fluorine Compounds*, ACS Monograph No. 155, Reinhold, N.Y., 1962.
485. W. A. Sheppard and C. M. Sharts, *Organic Fluorine Chemistry*, W. A. Benjamin, N.Y., 1969.
486. *Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, U.K., 1976.

487. G. Schiemann and B. Cornils, *Chemie und Technologie Cyclischer Fluorverbindungen*, F. Enke Verlag, Stuttgart, 1969.
488. *Handbook of Aromatic Fluorine Compounds*, Olin Corporation, Stamford, Conn., 1976.
489. R. D. Chambers, *Fluorine in Organic Chemistry*, John Wiley & Sons, Inc., New York, 1973.
490. E. Forche, "Houben-Weyl, Methoden der Organischen Chemie," in E. Mueller, ed., *Halogen-Verbindungen*, Georg Thieme Verlag, Stuttgart, 1962, 1–502.
491. R. Filler, in J. C. Tatlow, R. D. Peacock, and H. H. Hyman, eds., *Advances in Fluorine Chemistry*, Vol. **6**, CRC Press, Cleveland, Ohio, 1970, p. 1.
492. G. Fuller, *Manuf. Chem. Aerosol News* **35**, 43 (May 1964); *Ibid.* **35**, 45 (June 1964).
493. A. K. Barbour, L. J. Belf, and M. W. Buxton, in M. Stacey, J. C. Tatlow, and A. G. Sharpe, eds., *Advances in Fluorine Chemistry*, Vol. **3**, Butterworths, Washington, D.C., 1963, p. 181.
494. R. H. Shiley, D. R. Dickerson, and G. C. Finger, *Aromatic Fluorine Chemistry at the Illinois State Geological Survey*, circular 501, Urbana, Ill., 1978.
495. M. M. Boudakian, "Halopyridines," in R. A. Abramovitch, ed., *The Chemistry of Heterocyclic Compounds*, Vol. **14**, supplement part 2, *Pyridine and Its Derivatives*, Wiley-Interscience, New York, 1974, Chapt. 6, p. 407.
496. A. Roe, in R. Adams ed., *Organic Reactions*, Vol. **5**, John Wiley & Sons, Inc., New York, 1949, Chapt. 4, p. 193.
497. H. Suschitzky, in M. Stacey, J. C. Tatlow, and A. G. Sharpe, eds., *Advances in Fluorine Chemistry*, Vol. **4**, Butterworths, Washington, D.C., 1964, p. 1.
498. R. Filler and Y. Kobayashi, eds., *Biomedical Aspects of Fluorine Chemistry*, Kodansha, Tokyo, 1982.
499. R. E. Banks, D. W. A. Sharp, and J. C. Tatlow, eds., *Fluorine: The First Hundred Years*, Elsevier, Lausanne, 1986.
500. L. German and S. Zemzkov, eds., *New Fluorinating Agents in Organic Synthesis*, Springer-Verlag, Berlin, 1989.
501. I. L. Knunyants and G. G. Yakobson, eds., *Syntheses of Organic Fluorine Compounds*, Springer-Verlag, Berlin, 1985.
502. S. B. Walker, ed., *Fluorine in Agrochemicals*, Fluorochem, Ltd., Old Glossop, U.K., 1990.
503. R. E. Banks, ed., *Organofluorine Chemicals and Their Industrial Applications*, E. Horwood, Chichester, U.K., 1979.
504. R. E. Banks, ed., *Preparation, Properties and Industrial Applications of Organofluorine Compounds*, Ellis Horwood, Chichester, U.K., 1982.

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