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To Study the Effect of Fluoroalkylation of Organic Compounds

Shashank Shekhar Kapoor[1], Dr. Sukeerti Singh[2]

[1]Research Scholar, Sunrise University, Rajasthan
[2]Associate Professor, Sunrise University, Rajasthan

ABSTRACT

Information about the fluoroalkylation and perfluoroalkylation processes used in organic synthesis is rigorously examined, compiled, and explained. Examples are provided of the most practically significant characteristics of compounds with fluoroalkyl substituents. Consideration is given to the major developments and possibilities in this area of organic chemistry. Perfluoroalkyl compounds that are unavailable or experimentally challenging to make using conventional chemical methods are synthesized electrochemically. Processes using organometallic compounds and opportunities for the advancement of this field of study are given special consideration.

Keyword: Information, Fluoroalkylation, Perfluoroalkylation, Chemistry

INTRODUCTION

Because of their distinct physical and biological characteristics, organofluorine compounds find extensive application in agrochemistry, materials science, and medicine.Fluorine is now included in at least 30% to 40% of agricultural chemicals and 20% of pharmaceutical products that are sold, including three of the top eight medications in 2010. Nevertheless, only few of these substances have been found in the natural world. 4. By altering the dipole moment, overall reactivity, and the acidity or basicity of nearby groups, the substitution of fluorine, the most electronegative element, for hydrogen atoms modifies the molecule's steric and electronic characteristics. 2, 3 The synthesis of novel fluorinated compounds was first hampered by the need for certain conditions and processes due to the strong reactivity of elemental fluorine. Synthetic chemists began working in this direction once methods employing electrophilic fluorinating agents were developed. The development of new, improved, and more effective techniques for the synthesis of organofluorine compounds is anticipated to become a crucial field of study in the field of health since the development of new pharmaceutical medications will be correlated with the growing proportion of fluorinated molecules.

According to a recent empirical rule in pharmaceutical chemistry, adding fluorine to a possible drug molecule nearly tenfold increases the likelihood of achieving the target. The ability of fluorinated analogues to be identified by macromolecular binding by natural substrates provides several examples of the effectiveness of this approach. The creation of enzyme inhibitors or improving the stability of compounds against chemical degradation are two applications for fluorine's high electronegativity. 5. It was discovered that the anticancer, anti-viral, and anti-infectious qualities of approved medications or medications undergoing clinical trials—such as nucleosides, macrolides, alkaloids, steroids, amino acids, and prostaglandins—are significantly (by several orders of magnitude) improved by the addition of fluorine atoms or fluoroalkyl groups. The addition of CF3 and CnFm groups to second-generation epothilones (antitumor medicines) in the USA results in a 100-fold increase in cell growth inhibition while maintaining the drugs' lack of toxicity to the body.

Therefore, it is well acknowledged that fluorine derivatives play a role in a variety of sectors. The absence of practical and selective fluoroalkylation techniques that are resistant to different substituents, particularly in the last phases of complex molecule synthesis, is an issue. The current techniques for adding perfluoroalkyl groups to different substrata have a lot of problems and poor selectivity. The creation of a novel fluoroalkylation synthesis approach is undoubtedly a topical undertaking. Organometallic compounds may be used to achieve this goal. More than 30 years have passed since the initial attempts to synthesize fluoroalkylated organometallic compounds. Mercury trifluoromethyl compounds were among the first to be produced and were subsequently successfully employed for trifluormethylation. However, the range of their application is limited by the fact that organic mercury compounds are extremely poisonous and cause irreversible changes in the neurological system. Grignard reagents that are fluoroalkyl are extremely unstable at high temperatures. Although more stable than magnesium compounds, zinc fluoroalkyl reagents can be challenging to manufacture and isolate. They frequently serve as difluoromethylating and nucleophilic fluorinating reagents. Copper(I) compounds react over a wide temperature range and are relatively easy to prepare and separate. In copper-based trifluoromethylation, the main challenge

is the production of perfluoroethyl derivatives, which are challenging to separate during reaction mixture workup and purification.

Notably, trifluoromethylation and perfluoroalkylation catalytic reactions are extremely rare. While the first copper-catalyzed trifluoromethylation of aryl iodide was just reported in 2009, stoiometric reactions have been explored for a long time. Sadly, there are either relatively few or highly costly catalytic procedures that work well in this field. For instance, the cost of many ligands employed in Pd-catalyzed processes is frequently more than that of the metal. This is true for the ligand Brett Phos, which is employed in the sole Pd-catalyzed nucleophilic aromatic tri-fluoromethylation process that is currently accessible. Moreover, trifluoromethyl groups, as opposed to lengthy fluoroalkyl substituents, are appropriate for the majority of metal-promoted perfluoroalkylation processes. Ni-catalyzed trifluoromethylation and perfluoroalkylation were the subject of relatively few investigations. The difficulty of creating compounds with Ni—RF bonds (RF is the fluorine-containing group), their poor reactivity in oxidative addition and reductive elimination, and the ignorance of their redox properties—that is, how they might be activated toward the desired reactions—may all be contributing factors. It is necessary to advance metal complex methods for synthesizing organofluorine compounds using accessible catalytic processes.

The chemistry and applications of fluorine compounds

Because of Henri Moissan's efforts, who was the first to isolate elemental fluorine in 188±, fluorine chemistry emerged in the second half of the 19th century. Although research on fluorine reactions advanced slowly at first, the last few decades have seen the "fluorine boom," which is a result of the extraordinary significance and high value of products containing fluorine. Beginning with the discovery of Freons in the 1930s, which were employed as coolants, the chemistry of fluorine has been a major contributor to several noteworthy and quite diversified technological accomplishments over the past 80 years. The remarkable importance of the Manhattan Project (the creation of the A-bomb and hydrogen bomb) was connected to the area's future development. Nowadays, fluorine chemistry has developed into a vast field of science and technology that creates biologically active compounds with fluorine for use in pharmaceuticals, agrochemistry, coolants, fuels, surfactants, textile chemicals, polymers, dyes, and other materials. Many scientists have recently become interested in the growing importance of organofluorine compounds in a variety of fields. A "hot" research topic right now is the creation of novel techniques for the selective introduction of fluorine atoms and fluorine-containing groups into organic molecules in order to create biologically active chemicals and practical materials. Fluorine chemistry is a vast field of fundamental science interest because of the special structure-reactivity relationship shown for organofluorine molecules. Therefore, the combined efforts of basic and applied researchers produced the most significant scientific and technological advancements pertaining to fluorine chemistry.

The highest honor, the Nobel Prize in Chemistry, was given to some of the aforementioned accomplishments, although many more might potentially be deserving of this recognition. Observe the difference between 1979 and 2003 incidents. This does not imply that nothing noteworthy or noteworthy occurred within this time frame. The reason for this is that scientists have produced so many significant works over this time period (really the last 50 years) that it is nearly impossible to choose just one. The names of Academicians I L Hnunyants and A V Fokin, together with their successors, have become part of history, and Russia has made significant contributions to the development of fluorine chemistry and fluorine compounds. For Professor L M Yagupolskii (Ukraine), the same holds true. The expanding number of papers in this field attests to the significant and continuously rising interest in organofluorine chemistry (Fig. 1). - Fluorine is the thirteenth most abundant element in the Earth's crust, and it is found in the minerals fluorite, fluoroapatite, and cryolite. Nevertheless, to far, only 12 chemical compounds with a fluorine atom have been discovered in nature (Fig. 2). 9 (Note that one plant contains eight of these ω-fluorinated fatty acids. 9) Fluorine gives compounds with a fluorine atom certain characteristics. First, according to Table 1, fluorine is the element that is most electronegative. 8. Nearly every element can make a chemical connection with fluorine, and in many situations, the bond energies are very high.

The strongest link between carbon atoms is the C—F bond. Another unique characteristic of fluorine is its small atomic size; its van der Waals radius is only around 20% larger than that of hydrogen, making it the second-smallest substituent after hydrogen. In organic compounds, fluorine is the sole element that can be used in place of any number of hydrogen atoms. Organic fluorine compounds are often more stable chemically and thermally than their corresponding hydrocarbons because the C—F bond energy is higher than the C—H bond energy. Furthermore, low levels of intermolecular interactions for perfluorinated chemicals explain their easy sublimation (for solids) or evaporation (for liquids). Solid perfluorinated compounds have poor wettability and low adhesion, while liquid perfluorinated compounds have low surface tension due to weak intermolecular interactions. 10. Lastly, adding a fluorine atom or trifluoromethyl group makes the molecule more lipophilic, which improves the absorption of physiologically active compounds through biomembranes. 10. Because of all

these characteristics, organofluorine compounds are widely used in agriculture, medicine, and the creation of novel materials.

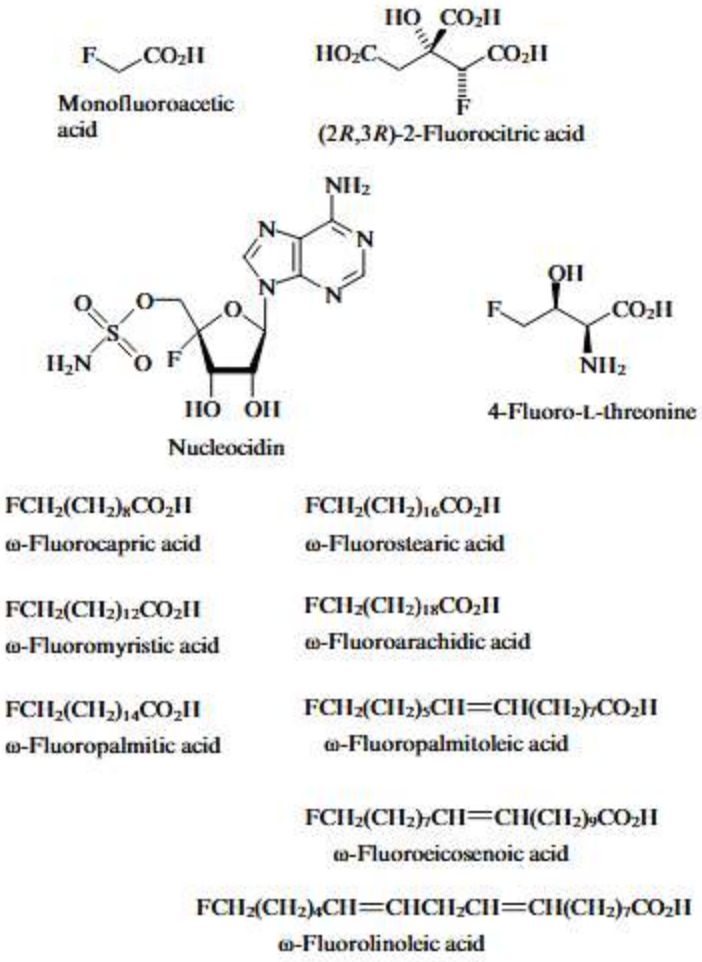


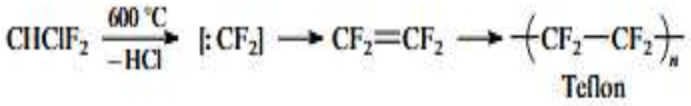
Figure 1. Naturally Occurring Organofluorine Compounds

Table 1. Comparative Characteristics of H, C, F And Cl Atoms

Parameter	Elements			
	H	**C**	**F**	**Cl**
Pauling electronegativity	2.2	2.55	3.98	3.16
van der Waals radius / Å	1.20	1.7	1.47	1.75
Length of the H3C—X bond / Å	1.087	1.535	1.382	1.785
Energy of the H3C—X bond /kcal mol^{-1}	103.1	88.0	108.1	81.1

At an American Chemical Society conference in the early 1930s, Thomas Midgley gave a study on organofluorine compounds as novel coolants. Midgley inhaled dichlorodifluoromethane (Freon 12, CCl2F2) and then exhaled it into an extinguished candle flame to illustrate the compound's characteristics. This remarkable event at the time sparked the investigation and later application of Freons. Hinetic Chemicals began producing Freon 12 and Freon 11 (CCl3 F) industrially in 1931. They then began producing tetrafluorodichloroethane (Freon 114, CClF2CClF2) in 1933. Difluorochloromethane (Freon 22) was first produced in 193±, whereas trifluorotrichloroethane (Freon 113, CCl2FCCl2F) was first produced in 1934.

Shortly after, it was discovered that pyrolysis of CHClF2 produces tetrafluoroethylene, which then polymerizes when stored at room temperature in an autoclave to produce polytetrafluoroethylene (Teflon).



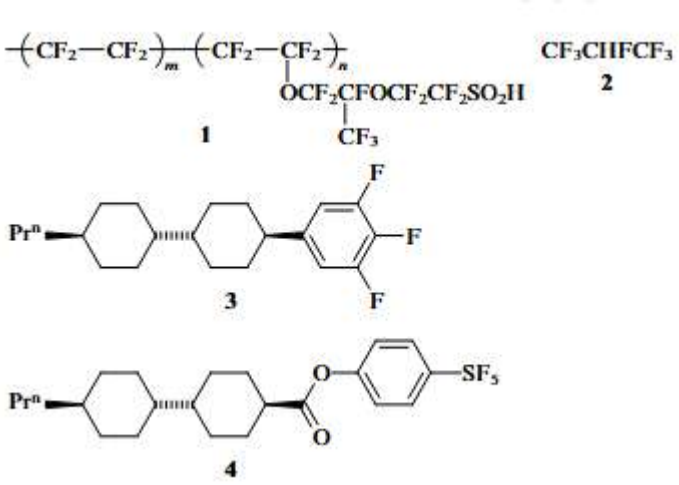
Since then, fluoropolymers have been widely used as elastomers, thermally stable plastics, coatings, membranes, and more because of their special qualities, which include high chemical and thermal stability, low surface energy, low combustibility, and superior biocompatibility.

Amorphous fluoropolymers are crucial for the production of optical fiber and microchips, whereas modern fluorinated polymers are widely used as a range of materials. Nafion (1) and other ion exchange polymers are frequently utilized as conducting membranes in fuel cells.

Since bromotrifluoromethane and bromochlorodifluoromethane do not conduct electricity, break down easily, and pose no threat to human health, they are used as effective fire extinguishing chemicals. However, because these agents are greenhouse gases that harm the ozone layer, their usage was outlawed in 2003. Instead, other fluorinated compounds, like heptafluoro-propane, were used.

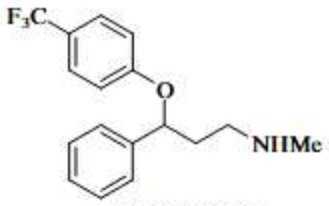
In order to produce contemporary TV sets and screens, organofluorine chemicals are essential. These compounds (such as compounds 3 and 4) are very valuable for the production of liquid crystals because, on the one hand, the presence of fluorine atoms in liquid crystals significantly affects the dielectric permittivity due to the strong electron-withdrawing ability of fluorine, and, on the other hand, it only slightly alters the molecular structure because of the small size of the fluorine atom.

Selected examples of the industrial and functional applications of organofluorine compounds are provided in this review section. Nonetheless, no other industry would use orgnofluorine chemicals as widely as pharmaceutics or medicine.

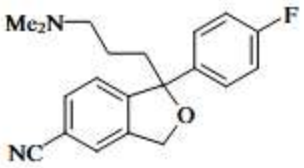


Approximately 150 of the many prescription medications on the market today include fluorine. Despite the limited quantity, these medications are extremely significant and frequently indispensable. The molecule's biological activity, binding to enzymes and receptors, and involvement in chemical metabolism are mostly caused by the fluorine atom's tiny size, high electronegativity, and low polarizability of the C—F bond. Drugs that include fluorine are used for a variety of reasons.

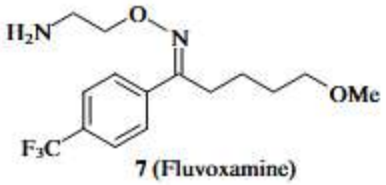
Compounds, for instance, are antidepressants that are members of the serotonin neurotransmitter class. Fluoxetine, also known as Prozac, is the main medication used to treat mental depression.



5 (Fluoxetine)



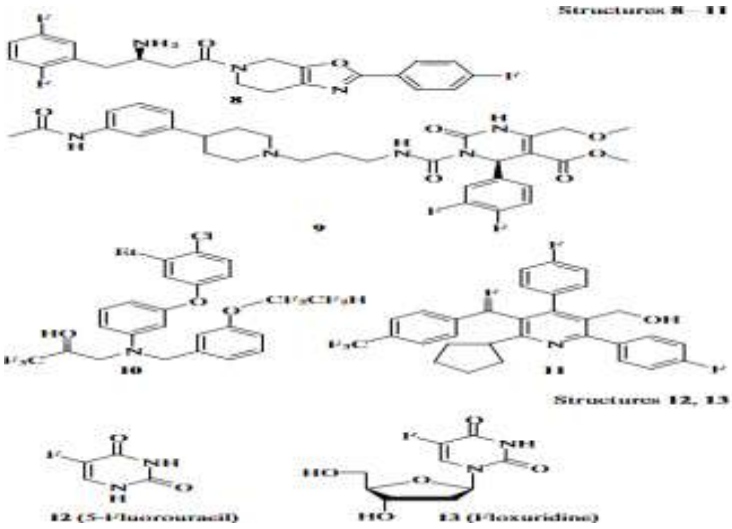
6 (Citalopram)



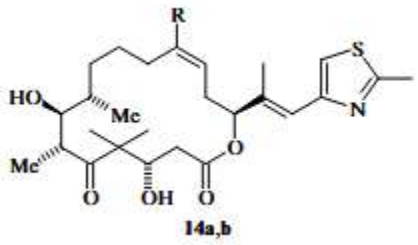
7 (Fluvoxamine)

Pharmaceutical agents are yet another class of substances that are used to treat metabolic and cardiovascular illnesses, including diabetes, hypertension, and obesity. Compound is a treatment for obesity, and thiazole (8) is used to prevent diabetes. Since fluorinated derivative of pyridine and disubstituted 3,3,3-trifluoro-2-hydroxypropylamine are cholesteryl ester transfer inhibitors, they are utilized to prevent cardiovascular disorders.

Lastly, anticancer drugs are arguably the most significant area of fluorinated chemical application in medicine. One of the earliest substances to be widely utilized for the prevention and treatment of different tumors were 5-fluoruracil, 5-fluoro-2'-deoxy-uridine and their derivatives.



Recently, a number of second-generation epothi-lones with exceptionally strong antitumor properties were created. It was discovered that adding a trifluoromethyl group to the methyl group of the deoxyepothilone B molecule (dEpoB, 14a) increases the drug's (Fludelone, 14b) ability to inhibit some tumor cells.



14a,b

R = Me (a, dEpoB), CF3 (b, Fludelone)

Examples of only a few medicinal substances with fluorine atoms are shown here. The number of these agents has been steadily rising in recent years. For instance, fluorine atoms or fluorinated groups were included in only 2% of all new pharmaceuticals in the 1970s; today, this number ranges from 30% to 40%. Therefore, developing techniques for introducing fluorine atoms and organofluorine groups into substrates is a topical challenge of modern chemistry. The commercialization of fluorinated structures still lags far behind experimental results, despite the growing demand for them. Companies that specialize in operations carried out under harsh conditions—which are typically necessary for fluorination—perform the majority of the large-scale syntheses of organofluorine compounds. Therefore, when creating pharmacological drugs, chemists should consider beforehand whether to include fluorinated building blocks in the structure. This has several unfavorable effects, such as limiting all synthesis conditions in later phases because of the fluorinated group and lowering product yield because of fluorine-related side reactions. There is a great need for new techniques for adding fluorine at the end of the synthesis process.

Table 2. Inhibition of The Tumour Cell Growth By Deoxyepothilone B And Fludelone

Histology	Tumour cell line	IC50 /nmol litre^{-1} (see [a])	
		dEpoB	Fludelone
Lung cancer	A549	3.9 0.4	3.7 2.4
Colon cancer	HT-29	7.2 2.2	4 1.7
	HCT-116	7.5 3.1	3.6 1.3
Breast cancer	MDA-MB-435	7.8 4.2	5.8 2.8
Ovarian cancer	IGROV	15 3.8	2 1.2
	SH-OV-3	13 4.7	1.6 0.5
	OVCAR-3	14 3.6	1.1 0.4
	OVCAR-4	16 2.5	1.8 0.7
Myeloma	RPMI-8226	36.7 2.0	7.6 1.2
	CAG	61.3 4.2	12.0 1.8
	OPM-2	38.9 3.3	8.2 2.2
	NCI-H929	42.7 4.5	9.2 1.9
	MOLP-5	68.6 5.5	14.4 2.6
Marrow stroma	HS-27a	100 10	102 8
	HS-5	100 8	96 7

[a] IC50 is the 50% inhibition concentration.

CONCLUSION

Fluoroalkyl-substituted 2-phenylpyridine is synthesized electrocatalytically at mild conditions and potentials that enable the formation of high oxidation states of complexed nickel and palladium. This reaction just requires the substrate and the electrocatalyst. More research is still being done on the mechanisms behind these redox reactions, with an emphasis on optimizing the range of potential substrates and the synthesis conditions. Recently, new research teams have been drawn to the ever-expanding importance of organofluorine compounds in a variety of scientific and practical domains. Chemical research is rapidly advancing in the development of novel techniques for the selective incorporation of fluorine atoms or fluorinated groups into organic molecules for the preparation of biologically active chemicals and the creation of various useful materials. Over the past ten years, a large number of reviews, book chapters, and original publications have been published on this topic. We clearly observe a "fluorine boom" and significant advancements in fluoroalkylation, initially facilitated by metals and metal complexes. By guaranteeing gentle synthesis conditions, high speeds and selectivity, and easy control over the processes by adjusting parameters like the potential and current density, electrochemical techniques bring up new possibilities. Research on perfluoroalkylation is ongoing, and the number of publications is growing like an avalanche. This is because of the results' high demand in many other fields of science and industry as well as the scientific interest in the topic. It is highly likely that we will see remarkable developments in this area of chemistry in the near future.

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