

The Fluorine Boom Continues as Benefits Become More Widespread

There has been a huge amount of interest in the production of fluorinated molecules which have applications in the pharmaceutical and agrochemical fields in recent years. There are very few compounds occurring in nature that contain fluorine, so it may seem strange that molecules containing fluorine have been used in preparing drugs and agrochemicals. The reasons for the surge in popularity of compounds containing fluorine can be explained based on its properties.

The high electronegative charge of fluorine causes a large electronic effect on neighboring carbon centers, and has an appreciable effect on the molecule's dipole moment and the acidity or basicity of other groups nearby, not to mention the molecule's overall reactivity and stability. The fluorine atom is larger than hydrogen. However; the additional steric demand caused by replacing a hydrogen atom with fluorine at receptor sites is low. The carbon-fluorine bond length is not much greater than carbon-hydrogen, which leads to little change in the steric bulk of the molecule. As far as drug molecules are concerned fluorine is usually more lipophilic than hydrogen, which makes the fluorinated compounds more fat soluble. This allows them to partition into membranes more easily and they have higher bioavailability.

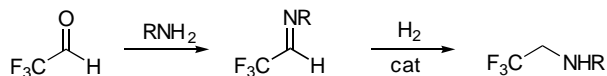
Several examples in the recent literature show that molecules useful as pharmaceuticals and agrochemicals have both fluorine and nitrogen atoms incorporated in their framework. Even with the additions of new fluorinating agents that have been developed over the past decades, the selective introduction of fluorine into molecules is far from easy, especially on the large scale necessary for production of pharmaceutical and agrochemical compounds. The most economical fluorinating agents are hydrogen fluoride and fluorine itself, which because of their volatility, reactivity and toxicity hazards are difficult to work with unless carried out by experts skilled in the art. There are some newer reagents, reactions involving them can be carried out under relatively mild conditions, require no special equipment and are designed to be simpler to handle compared to hydrogen fluoride and fluorine but they are significantly more expensive.

The advantage of having nitrogen atoms in drug molecules is well known and Halocarbon has now developed several fluorinated molecules that also contain a nitrogen functionality. This group of compounds now gives the drug designer the ability to incorporate the roles of both fluorine and nitrogen into the pharmaceutical structure in a single step. These groups of molecules help serve as building blocks to prepare more complex molecules. An added advantage is that the difficult fluorination step is done by experts who are well versed in the art. Halocarbon, for example, manufactures various fluorinated amines, amides, amino crotonates and nitriles.

These fluorinated molecules have been used to prepare compounds shown to possess interesting biological properties and their use has been cited in the recent literature. The following are a few examples.

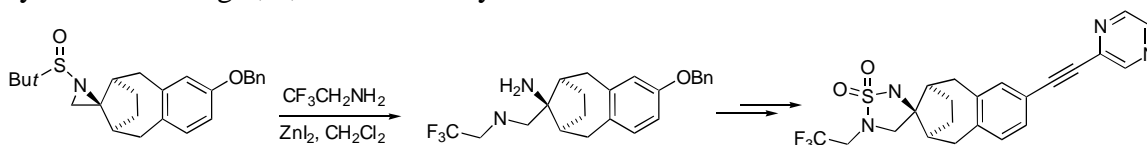
2, 2, 2-Trifluoroethylamine

One approach to making fluorinated amines involves the reductive amination of the corresponding carbonyl compounds. This process was demonstrated in U.S. Patent # 4,638,091 where trifluoroacetaldehyde was reacted with ammonia or a primary amine and the corresponding imine was hydrogenated using suitable hydrogenation methods to produce 2, 2, 2-trifluoroethylamine. Another method to prepare this compound involves the reduction of 2, 2, 2-trifluoroacetamide. This transformation can be accomplished using several reducing agents, for example LiAlH_4 .



Bowden, Roy; U.S. Patent 4,638,091; Imperial Chemical Industries PLC, 1987.

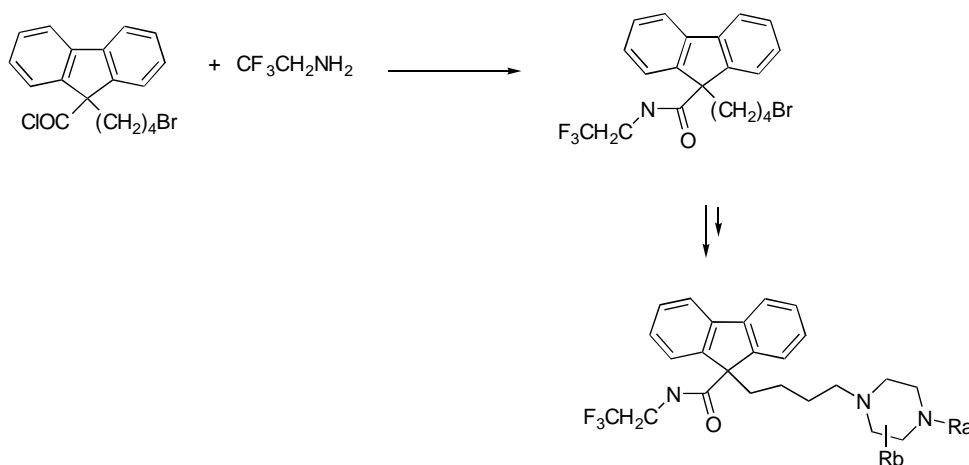
A molecule that has the potential to treat Alzheimer's disease has recently been synthesized using 2, 2, 2-trifluoroethylamine.



Alkynyl substituted spirocyclic sulfamides for the treatment of Alzheimer's disease:

Campbell, Alister et al. U.S. Patent # 7,041,688, Merck Sharp & Dohme Ltd. 2006.

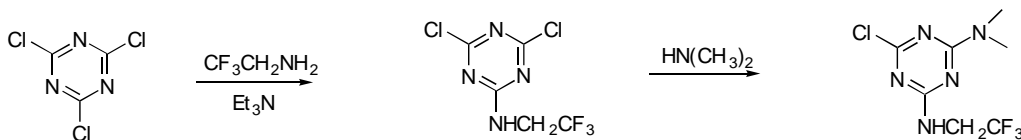
Another example where trifluoroethylamine has been used to prepare biologically active compounds is in the preparation of substituted piperazine derivatives which act as inhibitors of microsomal triglyceride transfer protein (MTP) and are useful in decreasing the plasma level of atherogenic lipoproteins.



Substituted piperazine derivatives, the preparation thereof and their use as medicaments:

Lehmann-Lintz, Thorsten et al. U.S. Patent # 6,818,644, Boehringer Ingelheim Pharm GmbH & Co. KG, 2004.

2, 2, 2-trifluoroethylamine has also been used as a raw material to prepare agricultural products. For example molecules containing 4, 6-diamino-s-triazines have been prepared for use as fluorinated herbicides.

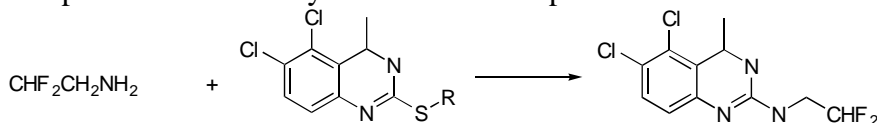


Herbicidally active fluorine containing 4, 6-diamino-s-triazines:

Kuhle, Engelbert et al. U.S. Patent # 4,459,151, Bayer Aktiengesellschaft, 1984.

2,2-Difluoroethylamine:

The neurotransmitter 5-hydroxytryptamine (5-HT) modulates a wide variety of physiological and pathological processes in the central nervous system and its periphery including anxiety, sleep regulation, aggression and depression (Hoyer et al., Pharmacol. Rev. 46, 157-204, 1994). A recent patent application uses the difluoro analog to prepare compounds with activity on the 5-HT receptor.

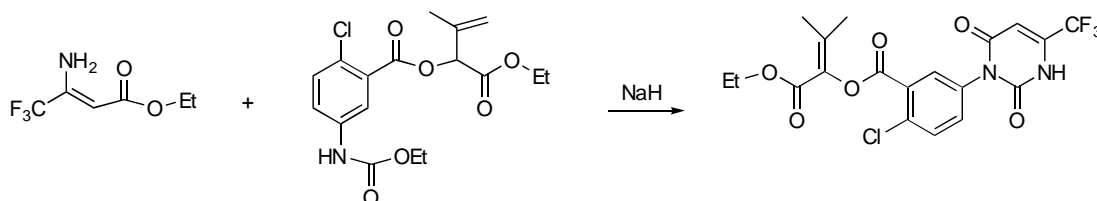


5-Chloro-4-alkyl-3,4-dihydro-quinazolin-2-ylamine derivatives:

Alanine, A et al. Patent Application # US 2006/0293349 A1, Hoffmann La Roche Inc.

Ethyl-3-amino-4, 4, 4-trifluorocrotonate

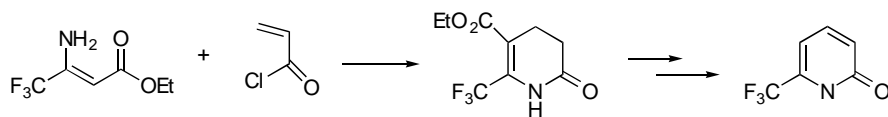
Another building block available from Halocarbon is ethyl-3-amino-4, 4, 4-trifluorocrotonate, which has been used to synthesize insecticidal and acaricidal agents (U.S. Patent # 6,548,511) and herbicides (U.S. Patent # 6,251,829).



Herbicidal benzoyloxy carboxylates and carboxamides:

Li, Bin et al. U.S. Patent # 6,251,829, Rohm and Haas Company, 2001.

This compound has also been used to prepare 6-trifluoromethyl-pyrid-2-one which is an intermediate in the preparation of pharmaceutical and agrochemical products as shown below.

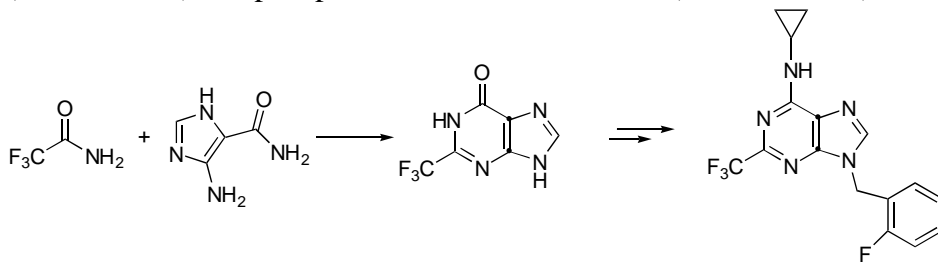


6-(trifluoromethyl)pyrid-2-one: Development and scale-up of a ring synthesis route based on trifluoroacetic anhydride:

Brown, Stephen et al. *Organic Process Research and Development*, 1987, 370-378.

2, 2, 2-Trifluoroacetamide

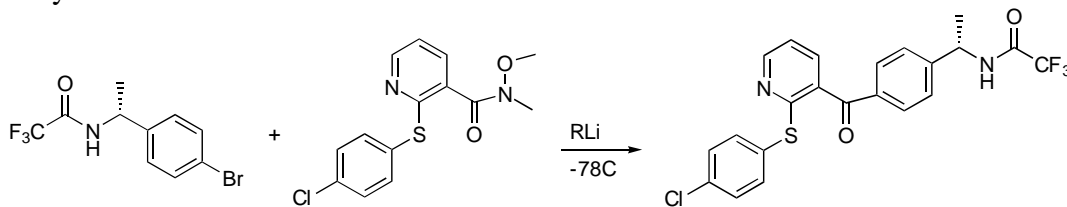
2, 2, 2-Trifluoroacetamide is another useful intermediate for the synthesis of fluorinated molecules. It can be treated with a variety of dehydration reagents to give the corresponding trifluoroacetonitrile or can be reduced with suitable reducing agents to afford the corresponding trifluoroethyl amine. It has been used to prepare herbicides, molecules which function as receptor agonists for treatment of metabolic disorders related to insulin resistance or hyperglycemia (WO0206232), pharmaceutical fungicides (WO0224619) and phosphodiesterase IV inhibitors (WO02098878).



2-Trifluoromethylpurines as phosphodiesterase IV inhibitors:

Liu, Ruiping et al. *WO 02098878*, Memory Pharmaceuticals, 2002.

Other substituted trifluoroacetamides have been employed as intermediates in synthesis of medicinally useful compounds that function as cannabinoid receptor agonists. These compounds exhibit anti inflammatory and immunomodulatory activity. The substituted trifluoroacetamides are prepared by reaction of suitable amine with trifluoroacetic anhydride.



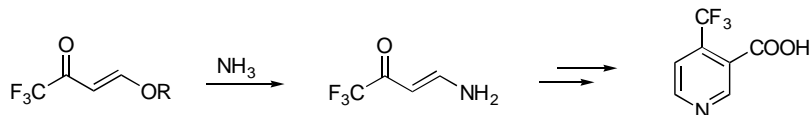
Cannabinoid receptor agonists:

Kozlowski, Joseph et al. *U. S. Patent # 7,217,732*, Schering Corporation, 2007

4-Alkoxy-1,1,1-trifluoro-3-butene-2-one

Trifluoromethyl nicotinic acid, which is a useful precursor for the synthesis of agricultural chemicals and pharmaceuticals, can be prepared from 4-amino-1,1,1-

trifluoro-3-butene-2-one, which can be prepared from 4-alkoxy-1,1,1-trifluoro-3-butene-2-one as shown below. The alkoxy-1,1,1-trifluoro-3-butene-2-one can be prepared by the reaction of trifluoroacetyl chloride with ethyl vinyl ether in the presence of a suitable organic base

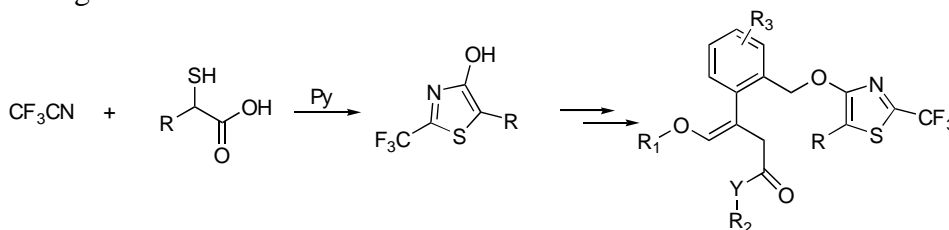


Process for producing 4-trifluoromethylnicotinic acid:

Koyanagi, Toru et al. U. S. Patent # 5,708,175, Ishihara Sangyo Kaisha Ltd. 1998.

Trifluoroacetonitrile

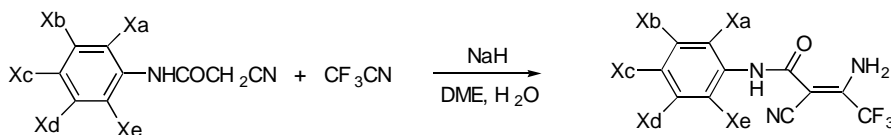
Another useful compound is trifluoroacetonitrile, which has been prepared by dehydration of 2,2,2-trifluoroacetamide. Trifluoroacetonitrile has been used to prepare various agrochemicals. An example of its use is to prepare thiazole derivatives that are useful as fungicides.



Thiazole derivatives with fungicidal activity:

Gusermoli, M et al. U. S. Patent # 7,166,620, Isagro Ricers S.r.l. 2007.

Another example is its use to prepare insecticides as demonstrated in the example shown below.



Crotonic acid amide derivatives and insecticides containing the same:

Hayashi, S et al. U. S. Patent # 5,066,657, SDS Biotech KK, 1991.

The above examples demonstrate the use of nitrogen containing fluorinated molecules as building blocks for biologically active molecules. In addition to the trifluoro compounds shown in these examples, Halocarbon also prepares the difluoro and bromo and chloro-difluoro analogs. We are pleased to offer these compounds to help meet the needs and goals of our customers.

