Chemistry of fluoroalkyl cyanides

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Abstract

This review is devoted to the chemistry of fluoroalkyl cyanides (R^F-nitriles): their synthesis and chemical properties. Syntheses of non-functionalized R^F-nitriles (FCH_2CN, F_2CHCN, CF_3CN, C_2F_5CN, FCH_2CH_2CN, etc.) and dinitriles (NCCHFCN, NCCF_2CN, NCCF_2CF_2CN, etc.) are considered. The synthesis of functionalized R^F-nitriles such as F_2NCF_2CN, F_2NCCIFCN, Cl_2CFCN, Br_2CFCN, (O_2N)_2CFCN, O_2NCF_2CH_2CH_2CN, and dinitriles, such as O(CF_2CN)_2, NCCF_2N=NCF_2CN, is also considered. R^F-Nitriles are attractive electrophilic, enophilic, and dienophilic building-blocks: they were used in the synthesis of various fluorine-containing heterocyclic compounds, such as R^F-bearing pyridines, 1,3,5-triazines, tetrazoles, and others. R^F-nitriles were also used in the synthesis of unusual acyclic compounds, such as fluoroalkylated N,N-difluoroamines, F_2NCF_2CF_2N=SF_2, R^F-imino esters, and others.

Keywords: Fluoroalkyl cyanides, fluoroalkyl nitriles, fluorination, cycloaddition, fluoroalkylated N,N-dihaloamines

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Table of Contents

1. Introduction
2. Synthesis of Fluoroalkyl Cyanides
   2.1. Dehydration of RF-amides
   2.2. Hydroamination of perfluoroalkenes
   2.3. Nucleophilic substitution of alkyl halides
   2.4. Synthesis from N,N-dihaloamines
   2.5. Synthesis from azidonitriles
   2.6. Reactions of alkenes and alkynes with N2F4
   2.7. Halogenation of nitriles
   2.8. Reaction of fluoroalkenes with HMDS
   2.9. Reaction of acyl cyanides with DAST
   2.10. Fluorination of active methylene nitriles
   2.11. Reactions of active methylene CF3-nitriles with electrophiles
   2.12. Addition of dichlorofluoroacetonitrile to alkenes
   2.13. Fluoroalkylation of aldehydes, imines, and enamines
   2.14. Syntheses of ethyl α-fluorocyanoacetate and its derivatives
   2.15. Synthesis of α-functionalized Rf-nitriles on the basis of Rf-ketones
   2.16. Other methods
3. Chemical Properties of Fluoroalkyl Cyanides
   3.1. Trimerization
   3.2. Reactions with Electrophiles
      3.2.1. Reactions with boron(III) and titanium(III) Lewis acids
      3.2.2. Reactions with NF3 and N2F4
      3.2.3. Reactions with halogens
      3.2.4. Reactions with chlorine fluorosulfate (ClOSO2F), SF4 and SCIF5
      3.2.5. Reactions with C-electrophiles
   3.3. Reactions with nucleophiles
      3.3.1. Reactions with O-nucleophiles
      3.3.2. Reactions with N-nucleophiles
      3.3.3. Reactions with C-nucleophiles
   3.4. Cycloadditions
   3.5. RF-nitriles as active methylene compounds
   3.6. Heterocyclizations of 3-amino-2,2-difluoro-2-propanenitriles with isocyanates and cyanoacetic acid
   3.7. Reduction
   3.8. Other reactions
4. Conclusions
5. Abbreviations
6. References
1. Introduction

Fluorinated organic compounds attract much interest due to their unique physicochemical properties, biological activities, and because they are of great importance in medicine. An electron-withdrawing R\( ^{F} \) group bonded to a carbon atom that belongs to a double or triple bond, or a conjugated system, significantly increases the electrophilic, dienophilic and dienic (in the case of a conjugated system) properties of the molecule. Fluoroalkyl cyanides (R\( ^{F} \)-cyanides, R\( ^{F} \)-nitriles) are a group of unique compounds, where a fluoroalkyl group is bonded to the highly polarized C≡N group. This fact dramatically increases the electrophilic as well as dienophilic properties of the C≡N group.

R\( ^{F} \)-cyanides (R\( ^{F} \)CN) can be divided into two groups: non-functionalized R\( ^{F} \)-cyanides and functionalized R\( ^{F} \)-cyanides. In non-functionalized R\( ^{F} \)-cyanides, the R\( ^{F} \) group contains only atoms of sp\(^{3} \) hybridized carbon, as well as atoms of fluorine and, optionally, hydrogen. In functionalized R\( ^{F} \)-cyanides, the R\( ^{F} \) group besides sp\(^{3} \)-C, F, and, optionally, H, contains at least one non-fluorine heteroatom or an sp\(^{2}(sp) \)-C (a double/triple bond). Those non-functionalized R\( ^{F} \)-cyanides, which don’t have a hydrogen atom in their R\( ^{F} \) groups, are perfluoroalkyl cyanides.

Trifluoroacetonitrile, CF\(_{3}\)CN, the parent perfluoroalkyl cyanide, is a symmetric top molecule. The measured dipole moment \( \mu = 1.262 \pm 0.010 \) D (measurements were made in a Stark-modulated microwave spectrometer). The enthalpy of formation of CF\(_{3}\)CN is \(-118.9 \) kcal/mol. The vibrational spectrum of this compound was originally assigned by Edgell and Potter. The lowest frequency vibrational mode of this molecule was measured at 192 cm\(^{-1} \) and is assumed to be the -C-C≡N bond. Owing to the large dipole moment and the large thermal population, the spectra are intense and it is relatively easy to observe spectra in the excited vibrational state \( v_{2} \) = 2. Physical properties of trifluoroacetonitrile such as critical temperature (311.11 K), critical pressure (524.75 lbf/ft\(^{2} \)), and critical density (0.470 g cm\(^{-3} \)) were measured. Thermodynamic properties of trifluoroacetonitrile from 12 K to its boiling point (-67.68 °C) were explored.

High resolution IR spectra over a range of temperatures from -80 to 250 °C of gaseous CF\(_{3}\)CN were published in 1970.

The rotational spectra of the ground state and some excited states of CF\(_{3}\)CN have been studied by several authors. The nuclear quadrupole hyperfine structure observed in the ground vibrational state has been the subject of Fourier transform work by Cox et al.

The rotational spectra of CF\(_{3}\)CN for transitions at \( J'' = 16, 18-21, \) and 32 (100–200 GHz) were recorded at -78 °C (P ~0.01 torr). These spectra are complex, similar to the spectra of CF\(_{3}\)C≡CH in the \( \nu_{10} \) = 2 state, having a superposition of three series for each \( J'' \) corresponding to \( l = 0 \) and \( l = \pm 2 \) (\( k/|l| > 0 \) or \( k < 0 \)).

The effect of electrode surface roughness on the breakdown characteristics of CF\(_{3}\)CN/CO\(_{2} \) gas mixtures was explored: these mixtures are considered as a potential alternative for replacing SF\(_{6} \) in high voltage power equipment.

The proton affinities of R\( ^{F} \)-nitriles such as CF\(_{3}\)CN (695 kJ/mol), CF\(_{3}\)CF\(_{2}\)CN (699 kJ/mol) and CF\(_{3}\)(CF\(_{2}\))\(_{2}\)CN (700 kJ/mol) were estimated.

R\( ^{F} \)-nitriles are able to form complexes with atoms and molecules, and adducts with anions. Thus, the rotational spectrum of the weakly bound (van der Waals) complex CF\(_{3}\)CN–argon has been observed and assigned. The structure of this complex is T-shaped with a center of mass separation of 3.73 Å. Centrifugal distortion analysis yields a weak bond stretching force constant of 1.92 Nm\(^{-1} \). The CF\(_{3}\)CN–H\(_{2}\)O complex has been studied by pulsed-nozzle Fourier transform microwave spectroscopy. The rotational constants, centrifugal distortion constants, and the \(^{14}\)N nuclear quadrupole coupling constants have been determined. The complex is T-shaped, with the oxygen atom of the water located 3.135 Å from the carbon atom of CF\(_{3}\) of
the CF$_3$CN molecule.\textsuperscript{25} Fluoride adducts of R\textsuperscript{F}-nitriles may be generated by bimolecular ion-molecule reactions. Calculated standard free energies (\(\Delta G^o\), kcal/mol) are: 21.9 for CF$_3$(F)=N\textsuperscript{ˉ}, 23.1 for C$_2$F$_5$(F)=N\textsuperscript{ˉ}, and 23.6 for CF$_3$CF$_2$CF(F)=N\textsuperscript{ˉ}.\textsuperscript{26}

\(\alpha\)-Functionalized R\textsuperscript{F}-nitriles are attractive intermediates in organic synthesis. \(\alpha\)-Nitro groups significantly increase the reactivity of \(\alpha\)-fluorinated nitriles. Thus, O$_2$NCF$_2$CN adds the CH$_3$ radical to the C≡N group four times as fast as CF$_3$CN, and (O$_2$N)$_2$CFCN is more reactive than O$_2$NCF$_2$CN.\textsuperscript{27}

The preparation of non-functionalized and functionalized R\textsuperscript{F}-nitriles involves a wide variety of synthetic methods. R\textsuperscript{F}-nitriles are excellent electrophilic, dienic, and dienophilic building-blocks: they were used in the synthesis of various fluorine-containing heterocyclic compounds, as well as unusual highly reactive acyclic compounds. Fluoroalkyl cyanides are important reagents for medicinal chemistry.

\textbf{2. Synthesis of Fluoroalkyl Cyanides}

\textbf{2.1. Dehydration of R\textsuperscript{F}-amides}

In 1922, Swarts described the preparation of trifluoroacetonitrile (N\textsubscript{1}) by dehydration of trifluoroacetamide (1) with phosphorus anhydride at 145-150 °C.\textsuperscript{28} In 1943, Gilman and Jones used essentially the same method for the preparation of trifluoroacetonitrile (74%), collected the product as a colorless liquid in a dry-ice-acetone trap (Scheme 1). The compound boiled at -63.9 °C (743 mm Hg).\textsuperscript{29} Similarly, difluoroacetonitrile, F$_2$CHCN, was prepared from difluoroacetamide and P$_4$O$_{10}$. This nitrile was isolated as a liquid that boils at 22 °C.\textsuperscript{30}

\begin{center}
\textbf{Scheme 1.} Preparation of trifluoroacetonitrile (N\textsubscript{1}) from trifluoroacetamide (1) and P$_4$O$_{10}$.
\end{center}

\begin{center}
\begin{align*}
\text{F}_3\text{C} & \quad \text{O} \\
\text{N} & \quad \text{H}_2 \\
\text{1} & \quad \text{P}_4\text{O}_{10} \\
\text{145-150 °C} & \quad \text{74\%} \\
\rightarrow & \quad \text{CF}_3\text{CN} \\
\text{N1} & \\
\end{align*}
\end{center}

The first synthesis of fluoroacetonitrile (N\textsubscript{2}) was published by Swarts in 1922 who claimed that it was necessary to distil the amide with phosphoric anhydride under reduced pressure and to collect the distillate at -50 °C.\textsuperscript{31} In 1949, Buckle \textit{et al.} used a similar approach to the synthesis of fluoroacetonitrile (65.2%) from fluoroacetamide (2) (Scheme 2), for its toxicity testing.\textsuperscript{32} The toxicity of fluoroacetonitrile on inhalation proved to be lower than that of methyl fluoroacetate because the nitrile is not hydrolyzed \textit{in vivo} to the toxic fluoroacetic acid.\textsuperscript{32-34}

\begin{center}
\textbf{Scheme 2.} Preparation of fluoroacetonitrile (N\textsubscript{2}) from fluoroacetamide (2) and P$_4$O$_{10}$.
\end{center}

\begin{center}
\begin{align*}
\text{F} & \quad \text{H}_2\text{C} & \quad \text{O} \\
\text{N} & \quad \text{H}_2 \\
\text{2} & \quad \text{P}_4\text{O}_{10} \\
\text{110-160 °C} & \quad \text{65.2\%} \\
\rightarrow & \quad \text{FCH}_2\text{CN} \\
\text{N2} & \\
\end{align*}
\end{center}

It was reported that fluoroacetonitrile (N\textsubscript{2}) can be synthesized from chloroacetamide (3) either via two separate procedures (a Finkelstein halogen exchange reaction with the formation of intermediate
fluoroacetamide (2) (67%) and a dehydration reaction that gives N2 in 82% yield) or via one-pot approach (70%) (Scheme 3).  

Scheme 3. Synthesis of fluoroacetonitrile (N2) from chloroacetamide (3).

Fluoropropionitrile (N3) (71%) was synthesized by heating amide 4 with P4O10 at 110-210 °C (Scheme 4).  

Scheme 4. Preparation of 3-fluoropropionitrile (N3) from 3-fluoropropioamide (4) and P4O10.

Different attempts have been undertaken to synthesize fluoromalononitrile through halogen-halogen exchange reaction by treating monobromomalononitrile with fluorinating agents.  

Scheme 5. Preparation of fluoromalononitrile (N4) from fluoromalonamide (6) and P4O10.
Dehydration of difluoromalonamide (7) with P₄O₁₀ at 210-220 °C gave difluoromalononitrile (N₅) in 30% yield (Scheme 6).  

![Scheme 6](image)

**Scheme 6.** Preparation of difluoromalononitrile (N₅) from difluoromalonamide (7) and P₄O₁₀.

Similarly, tetrafluorosuccinonitrile, NCCF₂CF₂CN (9%), hexafluoroglutaronitrile, NCCF₂CF₂CF₂CN, and octafluoroadiponitrile, NCCF₂CF₂CF₂CF₂CN (64%) were prepared from the corresponding fluorinated diamides and P₄O₁₀.  

The dehydration of trifluoroacetamide (1) under mild conditions (trifluoroacetic anhydride/pyridine) generates CF₃CN, which is transferred directly into the reactive medium. To effect the dehydration, (CF₃CO)₂O was dissolved in pyridine and cooled to room temperature prior to its addition to a solution of trifluoroacetamide. This exothermic premixing prevents the formation of volatile impurities contaminating the newly formed CF₃CN. The solution of CF₃CN was added through a dropping funnel to a solution of CF₃CONH₂ (Scheme 7).

![Scheme 7](image)

**Scheme 7.** Preparation of trifluoroacetonitrile (N₁) from trifluoroacetamide (1) and (CF₃CO)₂O.

The high-yield syntheses of CF₃CN N₁, C₂F₅CN N₆, and heptafluorobutyronitrile (N₇) under mild reaction conditions using readily available trifluoroacetamide (1), pentafluoropropionamide (8), heptafluorobutanamide (9), and trifluoroacetic anhydride were described (Scheme 8).

![Scheme 8](image)

**Scheme 8.** Dehydration of R⁻F-amides with (CF₃CO)₂O/Py.

Many other dehydrating agents can be used to transform R⁻F-amides into R⁻-nitriles. Thus, trifluoromethanesulfonic anhydride was used to transform trifluoroacetamide (1) into trifluoroacetonitrile (N₁) at 25 °C (Scheme 9).
Scheme 9. Dehydration of trifluoroacetamide (1) with (CF$_3$SO$_2$)$_2$O.

Difluoroamides 10-12 were transformed into the corresponding nitriles N8-10 in 77–91% yield upon treatment with POCl$_3$ in pyridine at 10 °C to rt (Scheme 10).

\[
\text{CF}_3\text{CONH}_2 \xrightarrow{(\text{CF}_3\text{SO}_2)_2\text{O}} \text{CF}_3\text{CN} \quad \text{(1)} \quad \text{N1}
\]

\[
\begin{array}{c}
\begin{array}{c}
\text{N}8 \quad \text{X} = \text{NMe} \\
\text{N9} \quad \text{X} = \text{NBn} \\
\text{N10} \quad \text{X} = \text{S}
\end{array}
\end{array}
\]

Scheme 10. Synthesis of α-functionalized α,α-difluoronitriles N8-10

Reaction of α-fluoroamide 13 with cyanuric chloride (14) afforded monofluorinated nitrile N11: the crude reaction mixture was subjected to oxidation with H$_5$IO$_6$/CrO$_3$ without prior purification, to give the desired N11 in isolated yields ranging from 38 to 42% (Scheme 11).

\[
\begin{array}{c}
\begin{array}{c}
\text{N11} \\
\text{N12}
\end{array}
\end{array}
\]

Scheme 11. Dehydration of amide 13 with cyanuric chloride (14).

2.2. Hydroamination of perfluoroalkenes

R^F-nitriles can be prepared through hydroamination of perfluoroalkenes. Thus, treatment of perfluoropropylene (15) with ammonia in aqueous dioxane resulted in the formation of α-hydroperfluoropropionitrile (N12) as the result of dehydrofluorination of intermediate amine 16 (Scheme 12).

\[
\begin{array}{c}
\begin{array}{c}
\text{N12} \\
\text{N12}
\end{array}
\end{array}
\]

Scheme 12. Hydroamination of perfluoropropylene (15).
Similarly, 3,3,3-trifluoro-2-(trifluoromethyl)propanenitrile (N13) was synthesized from perfluoroisobutylene (17) and NH₃ via the HF elimination from intermediate amine 18 (Scheme 13).47

![Scheme 13. Hydroamination of perfluoroisobutylene (17).](image)

2.3. Nucleophilic substitution of alkyl halides
Terminally monofluorinated nitriles, 7-fluoroheptanenitrile (N14) (90%) and 8-fluorooctanenitrile (N15) (76%) were synthesized from the corresponding fluorohaloalkanes 19 and NaCN (Scheme 14).34

![Scheme 14. Synthesis of terminally monofluorinated nitriles N14 and N15 via nucleophilic substitution.](image)

The reaction of 7-bromoheptanenitrile (20) with anhydrous KF in DEG gave 7-fluoroheptanenitrile (N16) in 58.3% yield (Scheme 15).34

![Scheme 15. Synthesis of 7-fluoroheptanenitrile (N16).](image)

2.4. Synthesis from N,N-dihaloamines
Irradiation (253.7 nm) of cyclopropane with tetrafluorohydrazine, N₂F₄, resulted in a complex mixture including F(CH₂)₃NF₂ (21) and F(CH₂)₂CN (N17), and the last is the result of dehydrofluorination of 1-difluoramino-3-fluoropropane (21) in its excited state [F(CH₂)₃NF₂]* 21* (Scheme 16).48

![Scheme 16. Formation of 3-fluoropropanenitrile from F(CH₂)₃NF₂ 21 in its excited state [F(CH₂)₃NF₂]* 20*.](image)

It was found that triphenylphosphine reacts smoothly with R⁰⁻N,N-difluoroamines 22 and 23 in a 2:1 stoichiometry to afford the corresponding R⁰⁻nitriles N1 and N18 in 80-90% yield. The reaction is rapid, free of side products (Scheme 17).49
Scheme 17. Synthesis of R^f-nitriles N1,N18 from R^f-N,N-difluoroamines 22,23.

The reaction of N,N-dichloro(pentafluoroethyl)amine (24) with Me3SiH at -25 °C resulted in the formation of unstable imidoyl fluoride 25. Decomposition of 25 to trifluoroacetonitrile (N1) is complete after about 12 min at ambient temperature (Scheme 18).

Scheme 18. Preparation of trifluoroacetonitrile (N1) from N,N-dichloro(pentafluoroethyl)amine (24).

The reaction of α,ω-bisdifluoriamine (26) with Ph3P in benzene at room temperature afforded R^f-dinitrile of formula O(CF2CN)_2 N19 in 90% yield (Scheme 19).

Scheme 19. Synthesis of O(CF2CN)_2.

2.5. Synthesis from azidonitriles

It was shown that azidonitriles 27 react with NO"BF_4^-" to produce R^f-nitriles N17,N14,N20-29 in nearly quantitative yields. Results from the reactions of a series of azidonitriles 27 with NO"BF_4^-" in CDCl_3 are given in Table 1. The nature of the reaction and the extent of rearrangement serve to classify this fluoride transfer process as involving carbenium ion intermediates. However, since fluoride substitution does not occur in similar reactions of NO"BF_4^-" with monofunctional alkyl azides, the authors of the research suggested that fluoride transfer cannot be represented simply as an intermolecular reaction of the tetrafluoroborate anion with a carbenium ion. The nitrile group is involved in the fluoride transfer process in the suggested mechanism.

Some amounts of H_2O (1-2 equiv) added to the nitrosonium salt prior to the azidonitrile produced an observable increase in the rate of gas evolution but did not measurably affect the reaction products. Treatment of 4-azidobutanenitrile (27a) with nitrosonium hexafluoroantimonate, NO"SbF_6^-", in deuterochloroform containing 1.0 equiv of H_2O resulted in the product distribution given below (Scheme 20).
Table 1. Product yields from reactions of azidonitriles 27 with NO\(^+\)BF\(_4^-\) in CDCl\(_3\) at 25 °C\(^{51}\)

| Entry | n  | R\(^{\ell}\)-nitriles | Yield, % | F(CH\(_2\))\(_n\)CN | CH\(_3\)CHF(CH\(_2\))\(_n\)CN | CH\(_3\)CH\(_2\)CHF(CH\(_2\))\(_{n-2}\)CN | BF\(_3\) |
|-------|----|------------------------|----------|-------------------|-----------------------------|----------------------------------|----------|
| 1     | 2  | N17, N22, N26          | 100      |                  |                             |                                  |          |
| 2     | 3  | N20, N23, N27          | 40       | 60               |                             |                                  |          |
| 3     | 4  | N21, N24, N28          | 22       | 78               |                             |                                  |          |
| 4     | 6  | N14, N25, N29          | 30       | 45               |                             | 25                               |          |

Scheme 20. Product distribution after treatment of 4-azidobutanenitrile (27a) with NO\(^+\)SbF\(_6^-\)

4-Azidobutanenitrile (27a) reacted three-times slower with NO\(^+\)BF\(_4^-\) to give N20 (32%), N23 (61%), 3-butenenitrile (28) (6%), and 2-butenenitrile (29) (1%). Nitrosonium hexafluorophosphate, NO\(^+\)PF\(_6^-\), was slightly more reactive than NO\(^+\)BF\(_4^-\) towards 4-azidobutanenitrile yielding N20 (18%), N25 (72%), 28 (7%), and 29 (3%).\(^{51}\)

It was noted\(^{51}\) that these results suggest that fluoride transfer from complex fluoride anions occurs through association of the developing Lewis acid with the basic nitrile group, as described in Scheme 21. The reactivities of nitrosonium salts with azidonitriles follow the order of Lewis acidities of the developing Lewis acids (SbF\(_5^+\)>PF\(_6^+\)>BF\(_3^+\)), and indicate a requirement for association of these developing acids with the nitrile group during nitrosation.\(^{51}\) Water acts to complex with the developed Lewis acid, decreasing the degree of association of the Lewis acid with unreacted azidonitrile 27.\(^{51}\)
Extensions of this nitrosative fluoride substitution process were reported. Nitrosative decomposition of azidonitriles 27 under the action of either NO$^+$BF$_4^-$, or NO$^+$PF$_6^-$, or NO$^+$SbF$_6^-$, gave mixtures fluoroalkyl cyanides and nonfluorinated substances.

Thus, reactions of these nitrosonium salts with 4-azidobutanenitrile (27a) at 25 °C produced mixtures of F(CH$_2$)$_3$CN N21, CH$_3$CHFCH$_2$CN N24, CH$_2$=CHCH$_2$CN 28, CH$_3$CH=CHCN 29, and trimethylenetetrazole (32) (Table 2).
Table 2. Product yields from nitrosative decomposition of 4-azidobutanenitrile (27a)\textsuperscript{52}

| Reactant       | F(CH\textsubscript{2})\textsubscript{3}CN | CH\textsubscript{3}CHFCH\textsubscript{2}CN | CH\textsubscript{2}H=CHCH\textsubscript{2}CN | CH\textsubscript{3}CH=CHCN | Yield, % |
|----------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|----------|
| NO\textsuperscript{+}BF\textsubscript{4}\textsuperscript{−} | 26                              | 37                              | 5                               | 4                               | 28       |
| NO\textsuperscript{+}PF\textsubscript{6}\textsuperscript{−} | 15                              | 61                              | < 1                             | < 1                             | 24       |
| NO\textsuperscript{+}SbF\textsubscript{6}\textsuperscript{−} | 4                               | 10                              | 10                              | 8                               | 68       |
| NO\textsuperscript{+}BF\textsubscript{4}\textsuperscript{−} + H\textsubscript{2}O | 38                              | 61                              | 1                               | < 1                             | < 1       |
| NO\textsuperscript{+}PF\textsubscript{6}\textsuperscript{−} + H\textsubscript{2}O | 18                              | 72                              | 7                               | 3                               | < 1       |
| NO\textsuperscript{+}SbF\textsubscript{6}\textsuperscript{−} + H\textsubscript{2}O | 15                              | 37                              | 36                              | 12                              | < 1       |
| NO\textsuperscript{+}BF\textsubscript{4}\textsuperscript{−} + BF\textsubscript{3} | 22                              | 16                              | < 1                             | < 1                             | 62       |
| NO\textsuperscript{+}SbF\textsubscript{6}\textsuperscript{−} + SbF\textsubscript{5} | < 1                             | < 1                             | < 1                             | < 1                             | 100      |

2.6. Reactions of alkenes and alkynes with N\textsubscript{2}F\textsubscript{4}

α-Functionalized R\textsuperscript{α}-nitriles are a large group of synthetically attractive building-blocks. (Difluoroamino)difluoroacetonitrile, compound N\textsubscript{30}, was synthesized in 80% yield through the reaction of 1,1-difluoroethylene (33) and tetrafluorohydrazine in the presence of KF (Scheme 22).\textsuperscript{53}

\[
\text{\begin{tikzpicture}
  \node [draw] (c) {33};
  \node [draw, right of=c] (d) {N30};
  \draw [->] (c) -- (d) node [midway, above] {N\textsubscript{2}F\textsubscript{4}, KF};
  \draw [->] (c) -- (d) node [midway, below] {160 °C};
  \draw [->] (c) -- (d) node [midway, right] {80%};
\end{tikzpicture}}
\]

Scheme 22. Synthesis of (difluoroamino)difluoroacetonitrile (N\textsubscript{30}) from 1,1-difluoroethylene (33) and N\textsubscript{2}F\textsubscript{4}.

Similarly, F\textsubscript{2}NCCI\textsubscript{4}N N\textsubscript{31} was synthesized from 1-chloro-1-fluoroethylene (34) and N\textsubscript{2}F\textsubscript{4} (Scheme 23).\textsuperscript{54}

\[
\text{\begin{tikzpicture}
  \node [draw] (c) {34};
  \node [draw, right of=c] (d) {N31};
  \draw [->] (c) -- (d) node [midway, above] {N\textsubscript{2}F\textsubscript{4}, KF};
  \draw [->] (c) -- (d) node [midway, below] {160 °C};
\end{tikzpicture}}
\]

Scheme 23. Synthesis of F\textsubscript{2}NCCI\textsubscript{4}N N\textsubscript{31}.

Treatment of dicyanoacetylene (35) with N\textsubscript{2}F\textsubscript{4} at 140 °C gave functionalized α-fluorodinitrile N\textsubscript{32} (Scheme 24).\textsuperscript{55}
Scheme 24. Synthesis of functionalized α-fluorodinitrile N32.

2.7. Halogenation of nitriles

Cesium fluoride promoted chlorination of cyanogen (36) with Cl₂ (1.2 equiv) at -60 to -20 °C gave Cl₂NCF₂CN N33 in 19% yield. Harsher conditions (-10 to -5 °C) and excess Cl₂ (1.5 equiv) increased the yield to 30% (Scheme 25). The catalytic effect of fluorides is based on the formation of the intermediate fluoride adducts (in this case, N≡C-C(F)=N⁻).56

Scheme 25. Cesium fluoride promoted chlorination of cyanogen (36) with Cl₂.

Reaction of Cl₂NCF₂CN N33 with Br₂ at 0 to 23 °C in the presence of NaF afforded difluoronitriles BrClNCF₂CN N34 (15%) and Br₂NCF₂CN N35 (~1%) (Scheme 26).56

Scheme 26. Bromination of Cl₂NCF₂CN N33 in the presence of NaF.

Bromination of perfluoroacrylonitrile (37) with Br₂ yielded 2,3-dibromo-2,3,3-trifluoropropanenitrile (N36) in 77% yield. Irradiation from an infrared lamp was required to start the reaction (Scheme 27).57

Scheme 27. Bromination of perfluoroacrylonitrile with Br₂.

2.8. Reaction of fluoroalkenes with HMDS

2H-hexafluoroisobutyronitrile (N13) was obtained in 52% yield by the reaction of HMDS with a large excess of perfluoroisobutylene (17) at 20 °C (Scheme 28).58
Scheme 28. Synthesis of 2H-hexafluoroisobutyronitrile (N13).

Similarly, α-functionalized β-trifluorinated nitrile N38 was synthesized in 40% yield from the corresponding fluoroalkene 38 (Scheme 29).  

Scheme 29. Synthesis of α-functionalized β-trifluorinated nitrile N38.

The same approach was used for the preparation of esters of 2-cyano-3,3,3-trifluoropropionic acid N39-41, which were synthesized in high yields from esters of perfluoromethacrylic acid 39-41 by reaction with HMDS (Scheme 30).

Scheme 30. Synthesis of β-trifluorinated nitriles N39-41.

2.9. Reaction of acyl cyanides with DAST

Reactions of acyl cyanides with DAST without a catalyst give α-difluorinated nitriles in low yields. Thus, treatment of acyl cyanides 42-48 with DAST gave α,α-difluoronitriles N42-48 in low yields (17-40%) (Scheme 31).
Scheme 31. Reaction of acyl cyanides 42-48 with DAST.

The reaction of benzoyl cyanide (49) with DAST gave 2-phenyl-2,2-difluoroacetonitrile (N49) in 20% yield. The same reaction conducted in the presence of ZnI$_2$ as a catalyst resulted in N49 in 65% yield (Scheme 32).

Scheme 32. Synthesis of 2-phenyl-2,2-difluoroacetonitrile (N49).

2.10. Fluorination of active methylene nitriles

Direct fluorination of sodio-dinitroacetonitrile (50) with F$_2$ in the presence of CaF$_2$ allows preparation of fluorodinitroacetonitrile (N50), which was isolated in 65% yield (Scheme 33).

Scheme 33. Synthesis of fluorodinitroacetonitrile (N50).

Electrophilic fluorination of benzyl nitriles 51-59 with NFSI (2.5 equiv) gave α,α-difluoronitriles N51-59 in 19-60% yield. In the case of 1.3 equiv of NFSI, monofluorinated nitrile N60 was obtained in 60% yield (Scheme 34).
Scheme 34. Synthesis of α-fluorinated nitriles N51-60.

Similarly, the precursor of estrone-3-sulfate analogues, difluoronitrile N61, was synthesized from benzylic nitrile 60 in 56% yield (Scheme 35).\textsuperscript{63}

Scheme 35. Synthesis of α,α-difluoronitrile N61.

α-Fluorination of active methylene nitrile 61 with NaH/Selectfluor in THF resulted in a mixture of monofluoro derivative N11 (32%), and difluoroamide by-product 62 (2.2:1 ratio, respectively), along with starting material (Scheme 36).\textsuperscript{46} Most likely, the formation of amide 62 is the result of the hydrolysis of the corresponding α,α-difluoronitrile, after the reaction mixture was quenched with aqueous NH\textsubscript{4}Cl.\textsuperscript{46}

Scheme 36. Synthesis of α-monofluorinated nitrile N11 from nitrile 61.

Monofluorinated nitrile N62 was synthesized in 45% yield from nitrile 63 and Bu\textsuperscript{′}Li/NFSI (Scheme 37).\textsuperscript{46}
Scheme 37. Synthesis of α-fluoronitrile N62.

Fluorination of diethyl cyanomethanephosphonate (64) with (CF$_3$SO$_2$)$_2$NF at -78 °C in THF in the presence of $n$-butyllithium afforded an α-functionalized α-fluoronitrile, diethyl cyanofluoromethanephosphonate (N63), in 51% yield (Scheme 38).64

Scheme 38. Synthesis of α-functionalized α-fluoronitrile N63.

Fluorination of ethyl α-cyanoalkanoates 65-73 with perchloryl fluoride, FClO$_3$, gives ethyl α-cyano-α-fluoroalkanoates N64-72 via intermediate salts 72. The synthesized N64-72 and their yields are shown in Table 3.65

Table 3. Fluorination of alkylated ethyl α-fluorocyanoacetate derivatives 65-73 with FClO$_3$65

| Entry | R         | Substrate | Product | Yield, % |
|-------|-----------|-----------|---------|----------|
| 1     | Me        | 65        | N64     | 35       |
| 2     | Et        | 66        | N65     | 80       |
| 3     | Pr        | 67        | N66     | 48       |
| 4     | Pr$i$     | 68        | N67     | 80       |
| 5     | Bu        | 69        | N68     | 47       |
| 6     | Bu$i$     | 70        | N69     | 78       |
| 7     | Bu$s$     | 71        | N70     | 46       |
| 8     | Bn        | 72        | N71     | 49       |
| 9     | EtOC(O)CH$_2$CH$_2$ | 73        | N72     | 71       |

2.11. Reactions of active methylene CF$_3$-nitriles with electrophiles

Reaction of N39 with trifluoronitrosomethane at -25 °C in the presence of a catalytic amount of Et$_3$N gave α-trifluoromethylated hydroxylaminonitrile N73 in 89.5% (Scheme 39).58
Scheme 39. Synthesis of α-trifluoromethylated hydroxylaminonitrile N73.

Reaction of N39 with S2Cl2 in MeCN at 20 °C in the presence of Et3N yielded another α-CF3-nitrile, bis-(α-carbomethoxy-α-cyanotrifluoroethyl)disulfide (N74) in 37.5% yield (Scheme 40).58

Scheme 40. Synthesis of bis-(α-carbomethoxy-α-cyanotrifluoroethyl)disulfide (N74).

Rf-nitriles N39 and N41, in the presence of a mild dehydrofluorinating reagent Et3N·BF3, at -10 °C quantitatively convert into CF3-dinitriles N75 and N76, respectively (Scheme 41).58

Scheme 41. Synthesis of CF3-dinitriles N75 and N76.

Reaction of α-CF3-nitrile N39 with fluorinated alkenes 39 and 17 in the presence of KF in MeCN at 20 °C afforded fluorinated nitriles N77 and N78, respectively, in 21.7-38.5% yield (Scheme 42).58

Scheme 42. Synthesis of fluorinated nitriles N77 and N78.

Mercurated CF3-nitrile N79 (91%) was prepared from N39 and mercuric acetate (Scheme 43).58
2.12. Addition of dichlorofluoroacetonitrile to alkenes

The addition of dichlorofluoroacetonitrile (N80) to methacrolein (75) in propionitrile at 110 °C in the presence of CuCl as catalyst and tributylphosphine/triethylamine as cocatalysts resulted in the formation of functionalized α-fluoronitrile N81 as a mixture of diastereomers (Scheme 44).37

![Scheme 44](image)

The addition of dichlorofluoroacetonitrile (N80) to methacrolein dimethyl acetal (76) resulted in a functionalized α-fluoronitrile, 2,4-dichloro-2-fluoro-4-methyl-5,5-dimethoxypentmenitrile (N82), which was obtained as a mixture of diastereomers in 87% yield (Scheme 45).37

![Scheme 45](image)

2.13. Fluoroalkylation of aldehydes, imines, and enamines

Fluoroalkylation of benzaldehyde with difluoro(trimethylsilyl)acetonitrile (N83) (its preparation is considered in paragraph 2.16, Scheme 51) in the presence of an activator gave difluoronitrile N84 as the major product and some amounts of N85 as the by-product, which is likely produced from the nucleophilic addition of N83 to primary product N84 (Table 4).66 After desilylative workup with KHF$_2$/CF$_3$CO$_2$H and column chromatography, the final product, α,α-difluoro-β-hydroxynitrile N86 was isolated in 82% yield (entry 9). The use of LiOAc as an activator gave N84 with 93-95% conversion and a minimum amount of by-product N85.66
Table 4. Fluoroalkylation of benzaldehyde with difluoro(trimethylsilyl)acetonitrile (N83)\(^{66}\)

\[
\begin{array}{cccccc}
\text{Entry} & \text{Activator} & \text{N83, equiv} & \text{Conditions} & \text{Conversion, %} & \text{N84:N85 ratio} \\
1 & \text{CsF, 10\%} & 1.3 & 0 ^\circ\text{C, 1 h} & 80 & 11:1 \\
2 & \text{TBAT, 10\%} & 1.3 & 0 ^\circ\text{C, 1 h} & 87 & 15:1 \\
3 & \text{Bu4NOAc, 10\%} & 1.3 & 0 ^\circ\text{C, 1 h} & 73 & 14:1 \\
4 & \text{NaOAc, 10\%} & 1.3 & 0 ^\circ\text{C, 1 h} & 18 & >30:1 \\
5 & \text{NaOAc, 10\%} & 1.3 & \text{rt, 24 h} & 96 & 14:1 \\
6 & \text{KOAoc, 10\%} & 1.3 & \text{rt, 18 h} & >98 & 6:1 \\
7^a & \text{KOAoc, 10\%} & 1.3 & 0 ^\circ\text{C, 2 h} & 84 & 5:1 \\
8 & \text{LiOAc, 10\%} & 1.3 & \text{rt, 24 h} & 78 & >30:1 \\
9 & \text{LiOAc, 50\%} & 2.0 & \text{rt, 18 h} & 93 (82^b) & >30:1 \\
10 & \text{LiOAc, 50\%} & 1.05 & 50 ^\circ\text{C, 3 h} & 95 (85^b) & >30:1 \\
\end{array}
\]

\(^a\)DMF as solvent. \(^b\)Isolated yield of N86.

The results of the fluoroalkylation of various aldehydes with difluoro(trimethylsilyl)acetonitrile (N83) in the presence of LiOAc are shown in Table 5.\(^{66}\)

Table 5. Reaction of aldehydes with Me₃SiCF₂CN N83\(^{66}\)

\[
\begin{array}{cccc}
\text{Entry} & \text{Aldehyde} & \text{Method} & \text{Product} \\
1 & \text{O}_{2}\text{N} & \text{A} & \text{N87} \\
2 & \text{O}_2\text{N} & \text{B} & \text{N88} \\
3 & \text{MeO} & \text{A} & \text{N89} \\
4 & \text{Me}_2\text{N} & \text{B} & \text{N90} \\
\end{array}
\]

Method A: N83 (2.0 equiv), rt, 18 h
Method B: N83 (1.05 equiv), 50 ^\circ\text{C, 3 h}
Table 5. Continued

| Entry | Aldehyde | Method | Product | Yield of product, % |
|-------|----------|--------|---------|--------------------|
| 5     | ![](image1) | B      | N91     | 84                 |
| 6     | ![](image2) | B      | N92     | 72                 |
| 7     | ![](image3) | B      | N93     | 73                 |
| 8     | ![](image4) | A      | N94     | 72                 |
| 9     | ![](image5) | A      | N95     | 72                 |
| 10    | ![](image6) | A      | N96     | 72                 |
| 11    | ![](image7) | B      | N97     | 70                 |
| 12    | ![](image8) | A      | N98     | 65                 |
| 13    | ![](image9) | B      | N99     | 66                 |

Fluoroalkylation of N-tosylimines with N83 in the presence of LiOAc allows preparation of α,α-difluorinated β-tosylaminonitriles N100-104, which were isolated in 76-93% yield (Table 6).66

Table 6. Preparation of α,α-difluorinated β-tosylaminonitriles N100-10466

| Entry | Imine | Time, h | Product | Yield of product, % |
|-------|-------|---------|---------|--------------------|
| 1     | ![](image10) | 18      | N100    | 93                 |
| 2     | ![](image11) | 48      | N101    | 78                 |
| 3     | ![](image12) | 18      | N102    | 91                 |
Table 6. Continued

| Entry | Imine | Time, h | Product | Yield of product, % |
|-------|-------|---------|---------|---------------------|
| 4     |       | 18      | N103    | 82                  |
| 5     |       | 48      | N104    | 76                  |

Fluoroalkylation of unactivated imines and enamines with N83 under acidic conditions in MeCN was explored, and N-monosubstituted (N105-107) and N,N-disubstituted (N108 and N109) α,α-difluorinated β-aminonitriles were isolated in 66-95% yield (Table 7).66

Table 7. Preparation of N-monosubstituted (N105-107) and N,N-disubstituted (N108 and N109) α,α-difluorinated β-aminonitriles66

| Entry | Substrate | Product | Yield of product, % |
|-------|-----------|---------|---------------------|
| 1     | [Structure] | N105    | 66                  |
| 2     | [Structure] | N106    | 68                  |
| 3     | [Structure] | N107    | 78                  |
| 4     | [Structure] | N108    | 95                  |
| 5     | [Structure] | N109    | 82                  |
2.14. Syntheses of ethyl α-fluorocyanoacetate and its derivatives

Treatment of α-hydroperfluoropropionitrile (N12) with NaOH in EtOH and then HCl resulted in a mixture of ethyl α-fluorocyanoacetate (N110) (60%) and ethyl fluoromalonate (77) (26%) as the result of the formation of perfluoroacrylonitrile as the key reactive intermediate.\(^{67}\) Ester N110 can be either hydrolyzed to α-fluorocyanoacetic acid (N111) or saponified to sodium α-fluorocyanoacetate (N112) (Scheme 46).\(^{67}\)

\[
\text{CF}_3\text{CHFCN} \quad \text{N12} \\
1. \text{NaOH, EtOH} \\
2. \text{H}_3\text{O}^+ \\
\rightarrow 60\% \\
\text{EtO} \quad \text{CN} \quad \text{O} \\
\text{F} \\
\text{N110} \\
\rightarrow 26\% \\
\text{EtO} \quad \text{F} \quad \text{O} \quad \text{Et} \\
\text{N111}
\]

\[
\text{NaO} \quad \text{CN} \\
\text{N112} \\
\rightarrow \text{NaOH} \\
\rightarrow \text{EtO} \quad \text{CN} \\
\text{N110} \\
\rightarrow \text{H}_3\text{O}^+ \\
\rightarrow \text{HO} \quad \text{CN} \\
\text{N111}
\]

**Scheme 46.** Synthesis of ethyl α-fluorocyanoacetate (N110), and α-fluorocyanoacetic acid (N111).

α-Fluoronitrile N110 reacts with various Michael acceptors giving highly functionalized α-fluorinated nitriles (Table 8).\(^{67}\)

**Table 8.** Preparation of derivatives of ethyl α-fluorocyanoacetate N111-116 via the Michael reaction\(^{67}\)

| Entry | Michael acceptor | Reaction time | Product | \(^{19}\)F NMR yield |
|-------|------------------|---------------|---------|---------------------|
| 1     | O                 | 10 min        | OCF(CN)CO₂Et | 79                  |
|       |                  |               | N111     |                     |
| 2     | MeO               | 2 h           | OCF(CN)CO₂Et | 95                  |
|       |                  |               | N112     |                     |
| 3     | MeO               | 2 h           | OCF(CN)CO₂Et | 94                  |
|       |                  |               | N113     |                     |
Table 8. Continued

| Entry | Michael acceptor | Reaction time | Product | 19F NMR yield |
|-------|------------------|--------------|---------|---------------|
| 4     |                  | 10 min       | CF(CN)CO₂Et | 99            |
| 5     |                  | 10 min       | CF(CN)CO₂Et | 93            |
| 6     |                  | 15 h         | CF(CN)CO₂Et | 92            |

2.15. Synthesis of α-functionalized R^F^-nitriles on the basis of R^F^-ketones

It was reported that the reaction of pentafluoronitroacetone (78) with hydrocyanic acid produces α-hydroxy-α-CF₃-nitrile N117, which was isolated in 73% yield (Scheme 47). Similarly, imines of R^F^-ketones can react with HCN producing the corresponding α-amino-α-R^F^-nitriles (see paragraph 3.3.3, Schemes 109, 113 and 114).

Scheme 47. Synthesis of α-hydroxy-α-CF₃-nitrile N117.

Gallium(III) triflate-catalyzed Strecker reaction of 1-mono-, 1,1-di-, and 1,1,1-trifluoracetone was published: α-amino-functionalized β-fluorinated nitriles N118-129 were synthesized in 84-97% yield using this method (Table 9).

Table 9. Synthesis of α-amino-R^F^-nitriles N118-129

| Entry | R^F | Amine | Product | Yield of product, % |
|-------|-----|-------|---------|---------------------|
| 1     | CH₂F| PhNH₂ | N118    | 97                  |
Table 9. Continued

| Entry | RF  | Amine     | Product                  | Yield of product, % |
|-------|-----|-----------|--------------------------|---------------------|
| 2     | CH$_2$F | Me-Ph-NH$_2$ | FH$_2$C-CN | 96 |
| 3     | CH$_2$F | Cl-Ph-NH$_2$ | FH$_2$C-CN | 92 |
| 4     | CH$_2$F | Br-Ph-NH$_2$ | FH$_2$C-CN | 90 |
| 5     | CHF$_2$ | PhNH$_2$   | F$_2$HC-CN | 94 |
| 6     | CHF$_2$ | Me-Ph-NH$_2$ | F$_2$HC-CN | 85 |
| 7     | CHF$_2$ | Cl-Ph-NH$_2$ | F$_2$HC-CN | 91 |
| 8     | CHF$_2$ | Br-Ph-NH$_2$ | F$_2$HC-CN | 89 |
| 9     | CF$_3$ | PhNH$_2$   | F$_3$C-CN | 95 |
| 10    | CF$_3$ | Me-Ph-NH$_2$ | F$_3$C-CN | 90 |
| 11    | CF$_3$ | Cl-Ph-NH$_2$ | F$_3$C-CN | 84 |
| 12    | CF$_3$ | Br-Ph-NH$_2$ | F$_3$C-CN | 95 |
2.16. Other methods

Reaction of \( N \)-fluoro-1-cyano-1-fluoromethanimine (79) with ClF resulted in the formation of difluoroacetonitrile derivative, nitrile ClFNCF\(_2\)CN (N130) (40%), together with Cl\(_2\)NCF\(_2\)CF\(_2\)NCIF (80) (58%) and other products (Scheme 48).\(^70\)

\[
\text{FN=CF(C)CN} \quad \xrightarrow{\text{ClF}} \quad \text{ClFNCF}_2\text{CN} + \text{Cl}_2\text{NCF}_2\text{CF}_2\text{NCIF} + \text{other products}
\]

\(-196\) to -50°C

\(79\)

\(N130\)

40%

\(80\)

58%

Scheme 48. Synthesis of ClFNCF\(_2\)CN (N130).

2-(Diethylamino)-2-(difluoromethyl)malononitrile (N131) was obtained in 91% yield through treatment of \( N,N \)-diethyl-1,1,2,2-tetrafluoroethanamine (81) with liquid HCN at 0 °C (Scheme 49).\(^71\)

\[
\text{HCF}_2\text{CF}_2\text{NEt}_2 \quad \xrightarrow{\text{liq HCN, 0 °C}} \quad \text{HF}_2\text{C} = \text{CN} \quad \text{CN} \quad \text{NET}_2
\]

\(81\)

91%

\(N131\)

Scheme 49. Synthesis of 2-(diethylamino)-2-(difluoromethyl)malononitrile (N131).

Free-radical addition of MeOH to perfluoroacrylonitrile (37) in the presence of benzoyl peroxide in a magnetically stirred autoclave at 75 °C afforded 2,3,3-trifluoro-3-methoxypropanenitrile (N132) (Scheme 50).\(^57\)

\[
\text{F}_2\text{C} = \text{CFCN} \quad \xrightarrow{\text{MeOH (PhCO)}_2} \quad \text{MeOCF}_2\text{CHFCN}
\]

\(37\)

75 °C

\(N132\)

Scheme 50. Synthesis of 2,3,3-trifluoro-3-methoxypropanenitrile (N132).

Free-radical alkylation at the fluorine-bearing carbon atom can be used for the synthesis of \( \gamma \)-fluorinated nitriles. Thus, the reaction of \( \alpha \)-fluoro-\( \alpha \)-nitroesters 82 and 83 with Bu\(_3\)SnH/CH\(_2\)=CHCN gave \( \gamma \)-fluoronitriles N133 and N134, respectively, in ca. 18% yield.\(^72\) Alternatively, Bu\(_3\)SnCH\(_2\)CH\(_2\)CN can be used as the source of the CH\(_2\)CH\(_2\)CN group.\(^72\) Similarly, \( \alpha \)-bromo-\( \alpha \)-fluoroesters can also be utilized in the synthesis of \( \gamma \)-fluoronitriles (Scheme 51).\(^72\)

\[
\text{EtO}_2\text{C} \quad \text{NO}_2 \quad \xrightarrow{\text{Bu}_3\text{SnH/CH}_2\text{=CHCN or Bu}_3\text{SnCH}_2\text{CH}_2\text{CN}} \quad \text{EtO}_2\text{C} \quad \text{CN}
\]

\(82, 83\)

ca. 18%

82,N133 R = CH\(_3\)COCH\(_2\)CH\(_2\)

83,N134 R = PhCH\(_2\)

Scheme 51. Synthesis of \( \gamma \)-fluoronitriles N133 and N134.
α-Silylated α-fluoronitrile \( \text{N83} \) (80%) was produced from silane \( \text{N84} \) by heating with trimethylsilyl cyanide in the presence of 5 mol.% of benzyltriethylammonium chloride (Scheme 52).\(^{66,73}\)

![Scheme 52. Synthesis of α-silylated α-fluoronitrile \( \text{N83} \).](image)

Acrylonitrile was used as the Michael acceptor in the reaction with difluoronitromethane (100-130 °C, sealed ampoule, EtONa or \( K_2CO_3 \) as a base), and 4,4-difluoro-4-nitrobutironitrile (\( \text{N135} \)) was obtained as the desired R\(^F\)-nitrile in 13% yield (Scheme 53).\(^{74}\)

![Scheme 53. Synthesis of 4,4-difluoro-4-nitrobutironitrile (\( \text{N135} \)).](image)

Phenylmercurated chloro(fluoro)acetonitrile \( \text{N137} \) was prepared in 53% yield through the reaction of chlorofluoroacetonitrile (\( \text{N136} \)) and \( Bu'OK \) with \( PhHgCl \) in THF at -70 °C (Scheme 54).\(^{75}\)

![Scheme 54. Synthesis of phenylmercurated chloro(fluoro)acetonitrile \( \text{N137} \).](image)

Photolysis of nitrile \( \text{N33} \) by Pyrex-filtered sunlight resulted in the formation of tetrafluorinated azonitrile \( \text{N138} \) (Scheme 55). Photolysis of nitrile \( BrClNCF_2CN \) \( \text{N34} \) produces the same azonitrile in 20% yield.\(^{56}\)

![Scheme 55. Photolysis of nitrile \( \text{N33} \).](image)

3-Fluoropropionitrile (\( \text{N3} \)) was prepared on a half-gram scale in a 92% yield by flash vacuum thermolysis of the 2-fluoroethylisocyanide (\( \text{N85} \)) at 650 °C. The product was collected in pure form in a U-trap equipped with stopcocks and immersed in a -90 °C bath (Scheme 56).\(^{76}\)
Scheme 56. Preparation of 3-fluoropropionitrile (N3) from 2-fluoroethylisocyanide (85).

Anodic monofluorination of nitriles 86 and 87 in MeCN in the presence of Et₃N·4HF resulted in monofluorinated nitriles N139 and N140, respectively, in 19-53% yield (Scheme 57).⁷⁷

Scheme 57. Anodic monofluorination of nitriles 86 and 87.

3. Chemical properties of fluoroalkyl cyanides

3.1. Trimerization

Heating trifluoroacetonitrile (N1) in the presence of other compounds often leads to trimerization and the formation of 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (88).⁷⁸,⁷⁹ Therefore, heating CF₃CN in the presence of reagents less reactive towards CF₃CN can cause the formation of some amounts of 88. Thus, CF₃CN doesn’t react with tetrafluorohydrazine, N₂F₄, at 100-220 °C, but in the presence of this reagent converts at these temperatures to triazine 88 in 100% yield (Scheme 58).⁷⁸ Similarly, in the presence on an imine, nitrile H(CF₂)₂CN gives some amounts of the corresponding HCF₂CF₂-triazine as a by-product (see paragraph 3.3.3, Scheme 102).⁷⁹

Scheme 58. Trimerization of trifluoroacetonitrile (N1).

3.2. Reactions with electrophiles

3.2.1 Reactions with boron(III) and titanium(III) Lewis acids. CF₃CN is a weaker donor than MeCN, and in contrast to the last, it forms no stable coordination compound with SnCl₄ or TiCl₄, and with the boron trihalides the insertion reaction occurs, giving dimeric ethyldieneaminoboranates 89 and 90 (Scheme 59).⁸⁰
Scheme 59. Formation of dimeric ethylideneaminoboranes 89 and 90.

It was also reported that fluoroacetonitrile (N2)\(^{81}\) and pentafluorpropionitrile (N6)\(^{82}\) react with boron Lewis acids forming dimer products of type 89.

The reaction of F\(_2\)NCClFCN N30 and F\(_2\)NCBrFCN N31 with BCl\(_3\) and BBr\(_3\) also leads to the formation of the corresponding dimeric products 91 and 92 (Scheme 60).\(^{54}\)

Scheme 60. Formation of dimeric products 91 and 92 from F\(_2\)NCClFCN N30 and F\(_2\)NCBrFCN N31.

Scheme 61. Synthesis of 1,1,1,4,4,4-hexafluoro-2,3-butadiimine (96).
It was shown that the reductive coupling of trifluoroacetonitrile (N1) with bis(cyclopentadienyl)titanium(III) chloride (93) resulted in the formation of corresponding μ-diimino titanium dimer 95 (through intermediate product 94). Treatment of dimer 93 with HCl/Et₂O liberated the free diimine, 1,1,1,4,4,4-hexafluoro-2,3-butanediimine (96) in 76% yield (Scheme 61).³³

### 3.2.2 Reactions with NF₃ and N₂F₄

Reactions of trifluoroacetonitrile (N1) with NF₃ at 515 °C gave a mixture of CF₃NF₂ (60%), CF₄ (15%), C₂F₆ (15%), and triazine 88 (10%). The reaction doesn’t proceed at 480 °C or lower temperatures (Scheme 62).³³

**Scheme 62.** Reaction of trifluoroacetonitrile (N1) with NF₃ at 515 °C

The suggested plausible mechanism of the formation of the above mixture of products involves the dissociation of the starting compounds at 515 °C to free radicals F₃C·, NC·, F·, F₂N·, and the recombinations of the latter.³³

Trifluoroacetonitrile (N1) doesn’t undergo the trimerization at room temperature and can react with various reagents. Thus, the reaction of CF₃CN with N₂F₄ at room temperature under UV light produces for 48 hours C₂F₅NF₂ 22 in 85% yield (Scheme 63).³³

**Scheme 63.** Synthesis of N,N-difluoro(perfluoroethyl)amine 22 from CF₃CN N1 and N₂F₄.

### 3.2.3 Reactions with halogens

The first direct fluorination of R⁻-nitriles was published in 1959.³⁴ Fluorination of CF₃CN and C₂F₅CN with F₂ diluted with helium resulted in the formation of a mixture of products. The fluorination of CF₃CN at 275 °C yielded a mixture of CF₄, C₂F₆, CF₃CF₂NF₂, and, probably, CF₂=NF. The fluorination of CF₃CN under milder conditions (30-47 °C) gave C₂F₆, F₅C₂N=NCF₂F₅, and unreacted CF₃CN. The fluorination of C₂F₅CN at 275 °C yielded a mixture of CF₄, C₂F₆, C₃F₈, and CF₃CF₂CF₂NF₂. The fluorination of C₂F₅CN under milder conditions (54-65 °C) gave F₇C₃N=NCF₃ and unreacted C₂F₅CN.³⁴

Direct fluorination of trifluoroacetonitrile with F₂/N₂ at 140 °C gave a mixture of CF₄, C₂F₆, C₂F₅NF₂, CF₃CF=NF, CF₃N=NC₂F₅, and C₂F₅N=NC₂F₅. The CF₃CF=NF was obtained pure by analytical chromatography.³⁵ Direct fluorination of CClF₂CN with F₂/N₂ at 140 °C yielded a crude product, which was rectified, and thus pure samples of CClF₂CF₂NF₂, CClF₂CF₂N=NCF₃, and CClF₂CF=NF were obtained.³⁵ The fluorination of CClF₂CN at 175 °C yielded a product, which contained CF₄, NF₃, CClF₃, C₂F₅Cl, and trace amounts of CF₃N=NCF₃, and CClF₂CF₂NF₂.³⁵
Direct fluorination of perfluorobutyronitrile (N7) with F$_2$/N$_2$ at 173-180 °C gave a mixture of perfluorobutane and N,N-difluoro(perfluorobutyl)amine (97) (43%) (Scheme 64).$^{40}$

$$\text{CF}_3\text{CF}_2\text{CF}_2\text{CN} \xrightarrow{\text{F}_2/\text{N}_2 \atop 173-180 \degree\text{C}} \text{CF}_3\text{CF}_2\text{CF}_2\text{CF}_3 + \text{CF}_3\text{CF}_2\text{CF}_2\text{CF}_3\text{NF}_2$$

Scheme 64. Direct fluorination of CF$_3$CF$_2$CF$_2$CN N7.

Direct fluorination of difluoromalononitrile, tetrafluorosuccinonitrile, and hexafluoroglutaronitrile with F$_2$/N$_2$ gives complex mixtures of fluorinated products. By the fluorination of tetrafluorosuccinonitrile, perfluoropyrrolidine was found as one of the products.$^{40}$

Indirect fluorination of such R'-nitriles as chlorodifluoroacetonitrile, difluoromalononitrile, tetrafluorosuccinonitrile, and hexafluoroglutaronitrile with argentifluoride was investigated.$^{86}$ Thus, the reaction of chlorodifluoroacetonitrile (N141) with excess AgF$_2$ gave 2,2-dichlorooctafluoroazoethane (98) in approximately 45% conversion (Scheme 65).$^{86}$

$$\text{ClCF}_2\text{CN} \xrightarrow{\text{AgF}_2 \atop 100 \degree\text{C}} \text{CClF}_2\text{CF}_2\text{N}=\text{NCF}_2\text{CClF}_2$$

Scheme 65. Fluorination of ClCF$_2$CN N141 with AgF$_2$.

The fluorination of difluoromalononitrile (N5) with AgF$_2$ at 100 °C proceeded not selectively producing a mixture of products such as CF$_4$, C$_2$F$_6$, CF$_3$CN, (CF$_3$)$_2$NF, and hexafluoro-1-pyrazoline (99) (15%) (Scheme 66).$^{86}$

$$\text{NCCF}_2\text{CN} \xrightarrow{\text{AgF}_2 \atop 100 \degree\text{C}} \text{CF}_4 + \text{C}_2\text{F}_6 + \text{CF}_3\text{CN} + \text{F}_3\text{C}_2\text{N}\text{CF}_3 +$$

$$\text{N}=\text{N}$$

15% 99

Scheme 66. Fluorination of difluoromalononitrile (N5) with AgF$_2$.

The fluorination of tetrafluorosuccinonitrile (N142) with AgF$_2$ at 100 °C gave a mixture of products such as C$_2$F$_6$, (CF$_3$)$_2$NF, perfluorocyclobutane, and perfluoropyrrolidine (100) (Scheme 67).$^{86}$

$$\text{NCCF}_2\text{CF}_2\text{CN} \xrightarrow{\text{AgF}_2 \atop 100 \degree\text{C}} \text{C}_2\text{F}_6 + \text{F}_3\text{C}_2\text{N}\text{CF}_3 +$$

$$\text{N}=\text{N}$$

100

Scheme 67. Fluorination of tetrafluorosuccinonitrile (N142) with AgF$_2$. 
The fluorination of hexafluoroglutaronitrile with AgF at 100 °C gave a mixture of CF₄, C₂F₆, C₃F₈, and (CF₃)₂NF as major components, and some (CF₃)₂NH.⁸⁶

Treatment of R⁻-nitriles with AgF and Cl₂ gave the corresponding polyfluoroazoalkanes (22-84%), however, other products frequently formed such as N-chlorofluoroalkylidenimines and N,N-dichlorofluoroalkylamines (Scheme 68).⁸⁷

\[
\text{R}^F\text{CN} \xrightarrow{\text{AgF/Cl}_2} \text{R}^F\text{CF}_2\text{N} = \text{NCF}_2\text{R}^F + \text{R}^F\text{CF} = \text{NCl} + \text{R}^F\text{CF}_2\text{NCl}_2
\]

22-84%

**Scheme 68.** Chlorination of R⁻-nitriles with Cl₂ in the presence AgF.

Photolytically induced reaction of CF₃CN with Cl₂ produced CF₃CCl=NCl, CF₃CCl=N=N=CClCF₃, and CF₃CCl₃ as well as minor quantities of CF₃C(Cl)=N-CCl₂CF₃, CF₃CCl₂C(CF₃)=N=N=C(Cl)CF₃, CF₃CCl₂-N=N=CCl₂CF₃, CF₃CCl₂C(CF₃)=N-CCl₂CF₃, and CF₃CCl₂C(CF₃)=N-N=C(CF₃)CCl₂CF₃.⁸⁸

Reaction of R⁻CN with ClF at -78 °C resulted in the formation of fluorinated aliphatic dichloramines R⁻CF₂NCl₂ in 65-95% yield (Scheme 69).⁸⁹

\[
\text{R}^F\text{CN} \xrightarrow{\text{ClF}} \text{R}^F\text{CF}_2\text{NCl}_2
\]

N1, N141, N6 65-95% 101, 102

**Scheme 69.** Reaction of R⁻CN with ClF.

Similarly, fluorinated tetrachlorodiamine Cl₂NCF₂CF₂CF₂NCl₂ 103 was synthesized from difluoromalononitrile (N5) and ClF (Scheme 70).⁹⁰

\[
\text{NCCF}_2\text{CN} \xrightarrow{\text{ClF}} \text{Cl}_2\text{NCF}_2\text{CF}_2\text{CF}_2\text{NCl}_2
\]

**Scheme 70.** Reaction of difluoromalononitrile (N5) with ClF.

The reaction of F₂NCF₂CN N30 with ClF proceeded easily in a stainless steel Hoke cylinder to give N,N-dichloro-N',N',1,1,2,2-hexafluoro-1,2-ethanediamine (104) in 80% yield (Scheme 71).⁵³

\[
\text{F}_2\text{NCF}_2\text{CN} \xrightarrow{\text{ClF}} \text{F}_2\text{NCF}_2\text{CF}_2\text{CCl}_2
\]

**Scheme 71.** Reaction of F₂NCF₂CN N30 with ClF.
Treatment of RF-nitriles with ClF/F₂ produced N-chloro-N-fluorofluoroalkylamines R^F CF₂ NClF 107 and 108 in yields above 90%. The mixture of RF-CN, ClF and F₂ was kept at 22 °C for 40 to 63 h. Under these conditions, ClF does not react with F₂ forming ClF₃, and F₂ does not react with RF-CN (Scheme 72).\(^{90,91}\)

![Chemical Structure](image)

**Scheme 72.** Synthesis of RF CF₂ NClF 107 and 108.

Chlorination and bromination of trifluoroacetonitrile (N1) in the presence of HgF₂ gave C₂F₅ NCl₂ 24 (94%) and C₂F₅ NBr₂ 109 (90%), respectively (Scheme 73).\(^{92,93}\)

![Chemical Structure](image)

**Scheme 73.** Chlorination and bromination of CF₃ CN N1 in the presence of HgF₂.

Bromination of CF₃ CN at 22 °C in the presence of CsF can produce in different proportions, dependently on the amount of Br₂, CF₃ CF=NBr and F₅ C₂ N=NC₂F₅.\(^ {94}\)

RF-nitriles N1,N6,N7 and N141 have been found to react readily with bromine and CsF at 16-23 °C to afford high yields of corresponding N-bromoimidoylfluorides 110-113.\(^ {95}\) Products 110-113 are the result of the oxidation of the RF CF=N⁻ anions with Br₂ (Scheme 74).\(^ {96}\)

![Chemical Structure](image)

**Scheme 74.** Bromination of RF-nitriles N1,N6,N7 and N141 with Br₂/CsF.
Cesium fluoride-promoted bromination of α,α-difluoronitrile Cl$_2$NCF$_2$CN N33 with excess Br$_2$ (1.5:10 mol. ratio) at -196 to 23 °C yielded N-brominated imidoyl fluoride 114, BrN=CFCF$_2$NBr$_2$, in 80% yield (Scheme 75).

![Scheme 75. Preparation of N-brominated imidoyl fluoride 114.](image)

A lower excess of Br$_2$ (1:2 mol. ratio) at -196 to 23 °C led to the following mixture of products: (BrN=CF)$_2$, (ClN=CF)$_2$, ClN=CFCF$_2$NCl$_2$, ClN=CFCF=NBBr, BrN=CFCF$_2$NCl$_2$, BrN=CFCF$_2$NBrCl, ClN=CFCF$_2$NBrCl, and ClN=CFCF$_2$NBr$_2$.

3.2.4 Reactions with chlorine fluorosulfate (ClOSO$_2$F), SF$_4$ and SCIF$_5$. Reaction of fluorodinitroacetonitrile (N50) with chlorine fluorosulfate in 1,1,2-trichlorotrifluoroethane (the solvent) at -25 to -20 °C resulted in N-chloroiminoflorodinitroacetyl fluorosulfate (115) (65%) (Scheme 76).

![Scheme 76. Synthesis of N-chloroiminoflorodinitroacetyl fluorosulfate (115).](image)

Similarly, other R$^F$-N-chloroiminofluorosulfates were synthesized from CF$_3$CN, CF$_3$OCF$_2$CN, CF$_3$(CF$_2$)$_2$CN, CF$_3$(CF$_2$)$_3$CN, and O$_2$NCF$_2$CN.

Reactions of F$_2$NCF$_2$CN N30 with SF$_4$/CsF at 100 °C and with SCIF$_5$ give imino-compounds 116 and 117, respectively (Scheme 77).

![Scheme 77. Reactions of F$_2$NCF$_2$CN N30 with SF$_4$/CsF and SCIF$_5$.](image)

3.2.5 Reactions with C-electrophiles. The reaction of fluoroacetonitrile (N2) with malonyl chloride gave 4-chloro-2-fluoromethyl-6-pyrimidone (124) in 65% yield. The suggested plausible mechanism involves the formation of diimidoyl chloride 119 and the subsequent cyclic transformations with the formation of intermediates 120-123 (Scheme 78).
Scheme 78. Reaction of fluoroacetonitrile (N2) with malonyl chloride (118).

No solid product was isolated when a mixture of cyanoacetyl chloride and N2 was kept at room temperature for several days.  

The reaction of fluoroacetonitrile (N2) with chloromalonyl chloride (125) gave 4,5-dichloro-2-fluoromethyl-6-pyrimidone (126) in 44% yield (Scheme 79).  

Scheme 79. Reaction of fluoroacetonitrile (N2) with chloromalonyl chloride (125).

The reaction of N2 with bromomalonyl chloride (127) gave a solid, which was crystallized from EtOH. The crystallized product was 4-chloro-2-fluoromethyl-6-pyrimidone (128) (32%) (Scheme 80). Most likely, EtOH in this case plays the role of a reducing agent (debromination).
Scheme 80. Reaction of fluoroacetonitrile (N2) with bromoromalonyl chloride (127).

3.3. Reactions with nucleophiles
3.3.1 Reactions with O-nucleophiles. The Pinner reaction of fluoroacetonitrile (N2) with propanol in the presence of HCl resulted in the corresponding ortho ester, 1-(2-fluoro-1,1-dipropoxyethoxy)propane (130) (through the formation of the intermediate iminoester hydrochloride 129), which was isolated in 27% yield (Scheme 81).100

Scheme 81. Reaction of fluoroacetonitrile (N2) with propanol.

Cyclic iminoester 131 was synthesized in 35% yield from N2 and 2-methyl-1,3-pentanediol in H2SO4 at -5 to 0 °C (Scheme 82).101 Oxazine 131 can be α-metalated rapidly at -78 °C by n-butyllithium, tert-butyllithium, or n-butyllithium/HMPA, and, moreover, 131 and its α-alkylated derivatives can be reduced with NaBH4, and thus can be used for the preparation of α-fluorinated aldehydes.101

Scheme 82. Synthesis of cyclic imino ester 131 from fluoroacetonitrile (N2).

The reaction of fluorodinitroacetonitrile (N50) with MeOH proceeds at 20 °C without any catalyst, whereas the corresponding reaction with less reactive 2,2-difluoro-2-nitroethanol was carried out in the
presence of Et₃N as a catalyst. In both cases, the corresponding imino esters 132 and 133 were isolated in 40% and 36% yield, respectively (Scheme 83).\textsuperscript{102}

![Scheme 83. Reaction of fluorodinitroacetonitrile (N50) with MeOH and 2,2-difluoro-2-nitroethanol.](image)

The reaction of highly functionalized alcohol 134 with CF₃CN in the presence of DBU was explored. Trifluoroacetimidate 135 was isolated in 85% yield (Scheme 84).\textsuperscript{103}

![Scheme 84. Synthesis of trifluoroacetimidate 135.](image)

Trifluoroacetimidates 140-143 were prepared from the corresponding alcohols 136-139 by treatment with n-butyllithium followed by addition of an excess of trifluoroacetonitrile (N1) at -78 °C in THF.\textsuperscript{104} Best yields were obtained using less than one mole equivalent of n-BuLi. The [3.3] rearrangements of 140-143 were then carried out by heating in xylene under reflux and gave the allylic trifluoroacetamides 144-147 in 35-90% yield (Scheme 85).\textsuperscript{104}
Various R^f-imidates 148-162 were synthesized through the reaction of in situ formed R^f-nitriles with benzyl alcohols in the presence of DBU. The obtained R^f-imidates were purified by silica gel column chromatography and were stable for a month at room temperature (Table 10). 105

**Table 10. Synthesis of R^f-imidates 148-162 from R^f-nitriles and benzyl alcohols**

| Entry | R^f          | Benzyl alcohol                  | Yield^a,b (%) | Imidate |
|-------|--------------|---------------------------------|---------------|---------|
| 1     | ClF_2C       | PhCH_2OH                        | 81 (40)       | 148     |
| 2     | ClF_2C       | 4-MeOC_6H_4CH_2OH               | 83             | 149     |
| 3     | ClF_2C       | 3,4-((MeO)_2C_6H_3CH_2OH        | 81 (36)       | 150     |
| 4     | F_3C         | PhCH_2OH                        | 64 (28)       | 151     |
| 5     | F_3C         | 4-MeOC_6H_4CH_2OH               | 85 (48)       | 152     |
| 6     | F_3C         | 3,4-((MeO)_2C_6H_3CH_2OH        | 81 (56)       | 153     |
| 7     | F(CF_2)_2    | PhCH_2OH                        | 78 (29)       | 154     |
| 8     | F(CF_2)_2    | 4-MeOC_6H_4CH_2OH               | 80             | 155     |
| 9     | F(CF_2)_2    | 3,4-((MeO)_2C_6H_3CH_2OH        | 82 (58)       | 156     |
| 10    | F(CF_2)_3    | PhCH_2OH                        | 77 (58)       | 157     |
| 11    | F(CF_2)_3    | 4-MeOC_6H_4CH_2OH               | 80             | 158     |
| 12    | F(CF_2)_3    | 3,4-((MeO)_2C_6H_3CH_2OH        | 70             | 159     |
| 13    | F(CF_2)_2    | PhCH_2OH                        | 74 (14)       | 160     |
| 14    | F(CF_2)_4    | PhCH_2OH                        | 76 (35)       | 161     |
| 15    | F(CF_2)_6    | PhCH_2OH                        | 90 (41)       | 162     |

^a Isolation yield after Kugelrohr distillation; ^b Parentheses show the yields in the absence of DBU.
Similarly, treatment of R\textsuperscript{F}-nitriles with (COCl\textsubscript{2})/DMSO in the presence of Et\textsubscript{3}N at -78 °C, and the subsequent treatment of the reaction mixtures with an alcohol in the presence of DBU resulted in the formation of various perfluoroimidates 163 in 27-92% yield (Scheme 86).\textsuperscript{106}

\[
\begin{align*}
\text{R}^{\text{F}} - \text{CN} &\xrightarrow{\text{Et}_3\text{N}, \text{CH}_2\text{Cl}_2, -78 \degree \text{C}} [\text{R}^{\text{F}}\text{CN}] \\
&\xrightarrow{\text{ROH, DBU, -78 \degree \text{C to rt}}} \text{R}^{\text{F}} - \text{OH}
\end{align*}
\]

\[\text{R}^{\text{F}} = \text{CF}_3, \text{CF}_2\text{Cl}, \text{C}_2\text{F}_5, \text{C}_3\text{F}_7\]

**Scheme 86.** Synthesis of various perfluoroimidates 163.

Reaction of R\textsuperscript{F}-nitriles with 1,2-epoxy-3-hydroxypropane (164) gave 2-R\textsuperscript{F}-4-(hydroxymethyl)oxazolines 166-168 (via intermediate R\textsuperscript{F}-imidates 165) in 46-93% yield (Table 11). BF\textsubscript{3}·Et\textsubscript{2}O can also be used as a catalyst to synthesize R\textsuperscript{F}-isoxazolines.\textsuperscript{107}

**Table 11.** 2-R\textsuperscript{F}-4-(hydroxymethyl)oxazolines 166-168\textsuperscript{107}

| Entry | \(\text{R}^{\text{F}}\) | Reaction temperature, °C | Product | Yield of product, % |
|-------|-----------------|--------------------------|---------|---------------------|
| 1     | CH\textsubscript{2}F | 70                       | 166     | 93                  |
| 2     | CHF\textsubscript{2} | 150                      | 167     | 56                  |
| 3     | CF\textsubscript{3}  | 150                      | 168     | 46                  |
The above \( R^F \)-isoxazolines 166-168 can be used in the synthesis of fluorine-containing analogues of 2-methyl-5-dimethylaminomethyl-2-oxazoline methiodide, which is the 2-oxazoline analogue of Fourbeau's dioxolane that equals acetylcholine in potency and belongs to the highly active cholinomimetics.\(^{108}\)

Heating 1-chloro-2,3-epoxypropane (169) with \( R^F \)-nitriles at 150 °C in a glass-pressure tube in the presence of tetraethylammonium bromide as the catalyst led to the formation of the corresponding \( R^F \)-oxazolines 172-174 in moderate yields.\(^{109}\) The suggested plausible mechanism involves the nucleophilic addition of intermediate 1-bromo-3-chloropropan-2-ol (170) to the activated cyano group of \( R^F \)CN and subsequent cyclization of anion 171 to give 172-174 (Scheme 87).\(^{109}\)

![Scheme 87. Reaction of 1-chloro-2,3-epoxypropane (169) with \( R^F \)-nitriles.](attachment:image)

The reaction of trifluoroacetonitrile (N1) with carboxylic acids was reported in 1963.\(^{110}\) Analytically pure imides: trifluoroacetyltrifluoroacetimide, (CF\(_3\))\(_2\)NH (176) and acetyltrifluoroacetimide, CH\(_3\)CONHCOCF\(_3\) (177), were synthesized from trifluoroacetonitrile (N1) and the corresponding carboxylic acids. The authors believe that the reaction of CF\(_3\)CO\(_2\)H with CF\(_3\)CN proceeds through four-membered cyclic intermediate 175 (Scheme 88).\(^{110}\) Imide 177 is a relatively unstable compound: it slowly decomposes to a mixture containing CF\(_3\)CO\(_2\)H and MeCN (Scheme 88).\(^{111}\)

![Scheme 88. Reaction of CF\(_3\)CN with CF\(_3\)CO\(_2\)H and AcOH.](attachment:image)
3.3.2 Reactions with N-nucleophiles. The reaction of R^F-nitriles with ammonia produces R^F-amidines 178, which then can react with R^F-CN in the reaction mixture to give products 179 (Scheme 89).  

\[
\text{R}^F\text{CN} \xrightarrow{\text{NH}_3} \text{R}^F\text{N}H\text{NH}_2 \quad \text{R}^F\text{CN} \xrightarrow{\text{NH}_3} \text{R}^F\text{N}H\text{NH}_2
\]

Scheme 89. Reactions of R^F-nitriles with ammonia.

The reaction of fluorodinitroacetonitrile (N50) with NH₃, and subsequent treatment of the reaction mixture with HCl gave the corresponding amidine hydrochloride 180 in 45.5% yield (Scheme 90).

\[
\begin{align*}
\text{(O}_2\text{N})_2\text{CF\text{C}} \xrightarrow{1. \text{NH}_3, -105 \text{ to } -70 \degree C} \text{O}_2\text{N}\text{NH} \xrightarrow{2. \text{HCl}} \text{O}_2\text{N}\text{NH}\text{HCl} \\
\text{N50} & \quad 45.5\% \\
\end{align*}
\]

Scheme 90. Synthesis of amidine hydrochloride 180.

Similarly, difluoronitroacetamidine, O₂NCF₂C(NH₂)=NH (63%) was synthesized from O₂NCF₂CN and ammonia.

Amidine 182 was prepared from amine 181, by treatment with trifluoroacetonitrile (Scheme 91).

\[
\begin{align*}
\text{Cl} \quad \text{N1} \quad \text{CF₃CN} & \quad \text{THF} \\
\text{181} & \quad \text{182} \\
\end{align*}
\]

Scheme 91. Preparation of amidine 182.

Reaction of F₂NCF₂CN N30 with ammonia at -196 to 25 °C yielded amidine 183, which was further transformed into triazine 184, whereas the reaction of N30 with hydrazine gave imidohydrazide 185 (Scheme 92).
Scheme 92. Reactions of F$_2$NCF$_2$CN N30 with ammonia and hydrazine.

Reaction of trifluoroacetonitrile (N1) with hydroxylamine generates trifluoroacetamide oxime (186) (Scheme 93), which then can be used for the synthesis of trifluoromethyl-1,2,4-oxadiazoles.$^{116}$

Scheme 93. Synthesis of trifluoroacetamide oxime (186).

Reaction of CF$_3$-enaminophosphonate 187 with fluoroalkylated nitriles gave R$^F$-substituted diisopropylamine-2,5-dihydro-1,5,2-diazaphosphinines adducts 188 and 189 in 80-49% yield.$^{117}$ R$^F$-substituted 2,5-dihydro-1,5,2-diazaphosphinines 190 and 191 (30-47%) can be prepared in their pure forms after treatment of 187 with MeLi at 0 °C, and then with an R$^F$-nitrile (Scheme 94).$^{117}$

Scheme 94. Reaction of CF$_3$-enaminophosphonate 187 with R$^F$-nitriles.
Aromatic (192) and heteroaromatic (193) β-enaminophosphonates reacted with perfluorooctanenitrile to give 2-ethoxy-2-oxo-4-phenyl- (194) and 2-ethoxy-4-(2-furyl)-2-oxo-6-(perfluoroheptyl)-2,5-dihydro-1,5,2-diazaphosphinine (195) in 52-45% yield (Scheme 95).  

\[ \text{R}^1 \text{POEt} \quad \text{NH} \quad \text{C}_7\text{F}_{16} \]

\[ 192,193 \quad \rightarrow \quad 194,195 \]

\[ i: 1. \text{BuLi/THF, 0 °C}; 2. \text{C}_7\text{F}_{16}\text{CN, 0 °C to rt}; 3. \text{H}_2\text{O} \]

\[ \text{192,194 R}^1 = \text{Ph} \]
\[ \text{193,195 R}^1 = \text{2-Furyl} \]

**Scheme 95.** Reaction of β-enaminophosphonates 192 and 193 with perfluorooctanenitrile.

### 3.3.3 Reactions with C-nucleophiles.

It was shown that the condensation of 1-acetylcyclohexanol (196) with trifluoroacetonitrile (N1) in the presence of ethylphenylaminomagnesium bromide results in the formation of α-hydroxyoxoenamine 197 (36 %) (Scheme 96).  

\[ \text{HO} \quad \text{C} \quad \text{N} \quad \text{PhN(Et)MgBr} \]

\[ \text{196} \quad \rightarrow \quad \text{197} \]

\[ \text{CF}_3\text{CN} \]

**Scheme 96.** Synthesis of α-hydroxyoxoenamine 197.

Acetylacetone (198) adds smoothly to the C≡N bond of trifluoroacetonitrile (N1) in the presence of catalytic amounts of nickel acetylacetonate, Ni(acac)$_2$, to give 1,1,1-trifluoro-2-amino-3-acetyl-2-penten-4-one (199) (98%), a functional enaminone. Upon action of K$_2$CO$_3$ in aqueous EtOH, 199 is deacetylated to give enaminone 200, which was isolated by sublimation in vacuum (Scheme 97).  

\[ \text{Me} \quad \text{C} \quad \text{O} \quad \text{Me} \]

\[ \text{CF}_3\text{CN} \quad \text{Ni(acac)}_2 \]

\[ 198 \quad \rightarrow \quad 199 \]

\[ \text{EtOH/H}_2\text{O} \quad \text{K}_2\text{CO}_3 \]

\[ 199 \quad \rightarrow \quad 200 \]

**Scheme 97.** Reaction of acetylacetone with CF$_3$CN in the presence of Ni(acac)$_2$.

Ethyl acetoacetate (201) readily reacts with CF$_3$CN in the presence of 1 mol.% of Ni(acac)$_2$ to give ethyl 2-acetyl-3-amino-4,4,4-trifluoro-2-butenoate (202) in 73% yield. The reaction occurs more slowly than in the case of acetylacetone (Scheme 98).
Scheme 98. Reaction of ethyl acetoacetate with CF$_3$CN.

It was reported that trifluoroacetonitrile (N1) reacts with diethyl malonate (203) in the presence of KOBu$^+$ in THF to give 2,6-bis(trifluoromethyl)-4-hydroxypyrimidine-5-carboxylate (204) in 88% yield.$^{121}$ In situ saponification of ion 206 with aqueous NaOH and subsequent treatment of the reaction mixture with HCl resulted in the formation of 2,6-bis(trifluoromethyl)-4-hydroxypyrimidine (208) in 72% yield (Scheme 99).$^{121}$

\[
\text{CF$_3$CN (N1), Ni(acac)$_2$} \quad \text{CH$_2$Cl$_2$} \quad \text{-20 °C} \quad 73\%
\]

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{OEt} \\
201 & \quad \text{CF$_3$N} & \quad \text{N} \\
& \quad \text{O} & \quad \text{OEt} \\
202 & \quad \text{H} & \quad \text{Me} \\
\end{align*}
\]

Scheme 99. Synthesis of CF$_3$-pyrimidines 204 and 208.

Cyclotrimerization of trifluoroacetonitrile (N1) and phenylacetonitrile in the presence of NaH in THF afforded 5-phenyl-2,6-bis(trifluoromethyl)pyrimidin-4-amine (209) in 46% yield (Scheme 100).$^{122}$
Scheme 100. Cyclotrimerization of CF₃CN and phenylacetonitrile in the presence of NaH.

Condensation of Rᵣ⁻-nitriles with imines was reported, and it was shown that trifluoroacetonitrile and 2,2,3,3-tetrafluoropropanenitrile react with aromatic methyl ketimines 210 and 211 producing the corresponding Rᵣ⁻-pyrimidines 213-216 (26-90%). Intermediate Rᵣ⁻-enaminoimines 212 were not isolated, while their CCl₃-analogue 217 was synthesized from imine 210 and trichloroacetonitrile in 74% yield. The reaction of CCl₃-enaminoimine with Rᵣ-CN gave CCl₃-bearing Rᵣ⁻-pyrimidines 218 and 219 in 60-87% yield (Scheme 101).

Scheme 101. Synthesis of Rᵣ⁻-pyrimidines from aromatic methyl ketimines and Rᵣ⁻-nitriles.

Reaction of aldimine 220 with H(CF₂)₂CN N143 gave a mixture of at least three products, but only triazine 221 (the trimerization product) was isolated in an analytically pure form (Scheme 102).

Scheme 102. Reaction of aldimine 220 with H(CF₂)₂CN.
Enamines 224, having an H-atom at the β-position, reacted with trifluoroacetonitrile (N1) at 40-80 °C, producing 2,4-bis(trifluoromethyl)pyrimidines 227. A plausible mechanism of this transformation involves the formation of intermediates 225 and 226 (Scheme 103).\textsuperscript{123,124}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme103.png}
\caption{Reaction of CF\textsubscript{3}CN with enamines 224.}
\end{figure}

It was reported that CF\textsubscript{3}-pyrimidinol 229 (84\%) was generated from ethyl cyanoacetate (228) utilizing both CF\textsubscript{3}CN from commercial cylinders and that formed \textit{in situ} (Scheme 104).\textsuperscript{42}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme104.png}
\caption{Synthesis of CF\textsubscript{3}-pyrimidinol 229.}
\end{figure}

Passing gaseous CF\textsubscript{3}CN into a solution of 3-oxopentanedioates 230 and 231 in EtOH containing excess aqueous AcONa provided CF\textsubscript{3}-pyridinediols 232 and 233 in poor to moderate yields (25-52\%) after an acidic workup.\textsuperscript{125} It was found that the best yields of 232 and 233 were obtained by passing CF\textsubscript{3}CN into a THF solution of 230 or 231 in the presence of 1 equiv of KOBu\textsuperscript{t}. The yields of 232 and 233 were good to excellent (57-95\%) by this procedure (Scheme 105).\textsuperscript{125}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme105.png}
\caption{Synthesis of CF\textsubscript{3}-pyridinediols 232 and 233.}
\end{figure}

Treatment of 234 with NaH followed by reaction of the resulting anion with trifluoroacetonitrile (N1) gave 5-cyano-6-(trifluoromethyl)uracil (236) in 75\% yield (Scheme 106).\textsuperscript{126}
Scheme 106. 5-cyano-6-(trifluoromethyl)uracil (236).

It was reported, that fluoroacetonitrile (N2) reacts normally with Grignard reagents, giving alkyl or aryl fluoromethyl ketones in 25-80% yield (Scheme 107).\(^\text{127}\)

\[ \text{FCH}_2\text{CN} \rightarrow \text{R}-\text{F} \]

Scheme 107. Synthesis of \( \alpha \)-fluoroketones 237-244 from FCH$_2$CN.

\textit{tert}-Butyl trifluoromethyl ketone 245 (54-82\%) was synthesized through the reaction between trifluoroacetonitrile (N1) and \textit{tert}-butylmagnesium chloride in the presence of CuCl (Scheme 108).\(^\text{128}\)

\[ \text{CF}_3\text{CN} \rightarrow \text{CF}_3 \]

Scheme 108. Synthesis of \textit{tert}-butyl trifluoromethyl ketone 245.

The reaction of trifluoroacetonitrile (N1) with PhMgBr resulted in the formation of phenyl trifluoromethyl ketimine 246 in 69\%.\(^\text{102}\) Imine 246 was used for the preparation of \( \alpha \)-amino-\( \alpha \)-(trifluoromethyl)phenylacetonitrile (N144), which is a good precursor for the synthesis of some
trifluoromethylated amino acids (Scheme 109). R\(^{F}\)-nitrile N144 is a potential reagent for \(^{19}\)F NMR determination of enantiomeric purity of acids.\(^{102}\)

\[
\text{CF}_3\text{CN} \quad \xrightarrow{\text{PhMgBr, ether, reflux}} \quad \text{NH} \quad \xrightarrow{\text{HCN}} \quad \text{Ph-C(CF}_3\text{)CN} \quad \text{NH}_2 \quad \text{N144}
\]

**Scheme 109.** Reaction of CF\(_3\)CN with PhMgBr and subsequent synthesis of R\(^{F}\)-nitrile N144.

It was found that apart from imines 246,248-250 (48-53%), 2-aryl-2,4,6-tris(trifluoromethyl)-1,2-dihydro-1,3,5-triazines 253-256 are formed (18–26%) in the reactions of CF\(_3\)CN with arylmagnesium bromides, due to the reaction of intermediate imine salt 247 with CF\(_3\)CN (Scheme 110).\(^{129}\) Excess CF\(_3\)CN increases the yield of dihydrotriazine 254 up to 66%.\(^{129}\)

\[
\text{CF}_3\text{CN} \quad \xrightarrow{\text{ArMgBr, Et}_2\text{O}} \quad \bigg[\text{CF}_3\text{N} = \text{NMgBr}\bigg] \quad \xrightarrow{\text{MeOH}} \quad \text{F}_3\text{C} = \text{NH} \quad \xrightarrow{\text{CF}_3\text{CN}} \quad \bigg[\text{CF}_3\text{N} = \text{NMgBr}\bigg] \quad \xrightarrow{\text{MeOH}} \quad \text{F}_3\text{C} - \text{N} = \text{NCF}_3 \quad \xrightarrow{\text{MeOH}} \quad \text{F}_3\text{C} - \text{N} = \text{NCF}_3
\]

246,253 Ar = Ph
248,254 Ar = 4-MeC\(_6\)H\(_4\)
249,255 Ar = 4-MeOC\(_6\)H\(_4\)
250,256 2-Me-5-FC\(_6\)H\(_3\)

**Scheme 110.** Synthesis of CF\(_3\)-imines 246,248-250 and dihydrotriazines 253-256.

Phenyllithium and 3-fluorophenylmagnesium bromide provided α-fluoroacetophenones 257 and 258 (88-86%) in the reaction with FCH\(_2\)CN N2. Aliphatic Grignard reagents gave the fluorinated ketones 259 and 260 in good yields (60-70%) (Scheme 111).\(^{130}\)
1,1-Difluoro-3-phenylpropan-2-amine (261) was synthesized from difluoroacetonitrile (N145) and benzylmagnesium chloride. Amine 261 was used for the synthesis of 3-(difluoromethyl)-1,2,3,4-tetrahydroisoquinoline (264), an inhibitor of phenylethanolamine N-methyltransferase (PNMT). Thus, compound 261 was treated with methyl chloroformate in CH$_2$Cl$_2$ and pyridine to afford carbamate 262. Cyclization of 262 with polyphosphoric acid yielded lactam 263 (70%), the key intermediate in the synthesis of potent PNMT. Reduction of 263 with BH$_3$·THF gave 3-(difluoromethyl)-1,2,3,4-tetrahydroisoquinoline (264) (70%) (Scheme 112).
Scheme 112. 1,1-Difluoro-3-phenylpropan-2-amine (261) and 3-(difluoromethyl)-1,2,3,4-tetrahydroisoquinoline (264).

Synthesis of 2-amino-2-fluoromethyl-3-pentenenitrile (N146) (30-51%), a key intermediate in the synthesis of 2,5-diamino-2-fluoromethyl-3(E)-pentenoic acid, an enzyme-activated inhibitor of ornithine decarboxylase activity, was reported. The approach is based on the reaction of fluoroacetonitrile (N2) with 1-propenylmagnesium bromide and the subsequent treatment of intermediate 265 with NaCN and NH₄Cl in H₂O (Scheme 113).

Scheme 113. Synthesis of α-fluoromethylated α-aminonitrile N146.

2-Amino-2-(fluoromethyl)-3-pentenenitrile (N147) was synthesized in 64% from fluoroacetonitrile (N2), propenylmagnesium bromide, and NaCN. Treatment of the reaction mixture formed after the addition of the Grignard reagent with NaBH₄ gave 1-fluoropent-3-en-2-amine (266) as a cis/trans mixture (13%) (Scheme 114).
Reaction of alkylphosphonates 267-269 with pentafluoropropionitrile (N6) at 0 °C leads to the formation of C2F5-substituted diisopropylamine-2,5-dihydro-1,5,2-diazaphosphinines adducts 270-272, which were isolated in 81-95% yield.117 The plausible mechanism involves the formation of intermediates 273-275 (Scheme 115).117

Scheme 114. Synthesis of monofluorinated α-aminonitrile N147 and fluoroamine 266.

Scheme 115. Synthesis of C2F5-substituted diisopropylamine-2,5-dihydro-1,5,2-diazaphosphinines adducts 270-272.
Dialkyl phosphites 276 and 277 reacted with difluoroacetonitrile and trifluoroacetonitrile in the presence of catalytic amounts of a nitrogen base at room temperature to form iminophosphonates 278-280 in high yields. In solution, imidoyl phosphonates 278-280 exist as equilibrium mixtures of the Z/E-isomers, the more sterically hindered Z-configuration being thermodynamically preferable. The Z/E ratio essentially depends on the R^F substituent at the C=N bond, but it is practically independent of the nature of the phosphonyl group (Scheme 116).

\[
\begin{align*}
\text{RO}_2\text{P}=\text{O} & \quad \text{R}^\text{F}\text{CN}, \text{Et}_3\text{N} \quad \text{rt, 7 days} \\
276 \; \text{R} = \text{Et} & \quad \text{R}^\text{F} = \text{CF}_3, \text{CF}_2\text{H} \\
277 \; \text{R} = \text{Pr} & \\
\end{align*}
\]

\[\text{278} \; \text{R}^\text{F} = \text{CF}_3; \; \text{R} = \text{Et}; \; \text{Z/E} = 10:1 \]
\[\text{279} \; \text{R}^\text{F} = \text{CF}_3; \; \text{R} = \text{Pr}; \; \text{Z/E} = 10:1 \]
\[\text{280} \; \text{R}^\text{F} = \text{CHF}_2; \; \text{R} = \text{Et}; \; \text{Z/E} = 5:1 \]

Scheme 116. Synthesis of imidoyl phosphonates 278-280.

Less nucleophilic diphenyl phosphite (281) reacts with fluorinated nitriles in the same manner to afford imidoyl phosphonates 282 and 283, as a dynamic mixture of Z/E-isomers. Iminophosphonates 282 and 283 undergo partial dissociation to the initial compounds on storage at room temperature. Diphenyl phosphite, formed upon dissociation, quickly adds to the activated C=N bond of the starting iminophosphonates to form stable geminal bisphosphonates 284 and 285, which are the desired products of this reaction (Scheme 117).

A series of trihaloacetonitriles, bearing a different number of fluorine and chlorine atoms in the molecule, were also investigated in the above reaction.

\[
\begin{align*}
\text{PhO}_2\text{P}=\text{O} & \quad \text{RFCN} \\
\text{281} & \\
\text{PhO} & \quad \text{PhO} \quad \text{R}^\text{F} \quad \text{NH}_2 \\
\text{282,283} & \\
\text{N1,282,284} & \text{R}^\text{F} = \text{CF}_3 \\
\text{N145,283,285} & \text{R}^\text{F} = \text{CF}_2\text{H} \\
\end{align*}
\]

Scheme 117. Formation of imidoyl phosphonates 282 and 283, and geminal bisphosphonates 284 and 285.

Optically pure CF₃-bearing dimethyl iminophosphonates (+)-286 and (-)-286 were prepared by the reaction of readily accessible (+)- and (-)-dimethyl phosphites with CF₃CN (Scheme 118).
Scheme 118. Synthesis of optically pure CF₃-bearing dimethyl iminophosphonates (+)-286 and (-)-286.

R²-nitriles undergo the Houben–Hoesch reaction with arenes in CF₃SO₃H to give α-fluorinated ketones in good yields.¹³⁰ The fluorine substituents appear to enhance the reactivities of the nitriles (and the nitrilium ion intermediates) compared to similar aliphatic nitriles.¹³⁰ Thus, FCH₂CN and F₂CHCN reacted with p-chloroanisole in the presence of trifluoromethanesulfonic acid and the respective ketones 287 and 288 were formed in good yields (63-74%). Other ketones bearing CH₂F, CHF₂ and CF₃ groups 289-292 were also synthesized in up to 98% yield by using of the corresponding aromatic substrates, CH₂FCN, CHF₂CN and CF₃CN (Scheme 119).¹³⁰

Scheme 119. Houben–Hoesch reaction of R²CN with arenes in CF₃SO₃H.

Besides fluorinated acetonitriles, several other types of R²-nitriles gave ketone products in moderate to good yields. α-Difluorinated nitrile N49 leads to ketone 293 (75%). R²-Dinitrile N148 provides the R²-1,6-diketone 294 (45%), while ketone 295 (88%) is formed from perfluoroocetanenitrile (N149) (Scheme 120).¹³⁰
Scheme 120. Houben–Hoesch reaction of R₅-nitriles with benzene in CF₃SO₃H.

3.4. Cycloadditions
Due to the presence in molecules of R₅-nitriles the highly polarized triple bond that belongs to the highly electron-deficient C≡N group, these compounds are reactive enophiles, dienophiles and dipolarophiles: they can undergo cycloadditions with isolated double bonds (including ylides) and conjugated systems. Fluoroalkyl substituted N-vinylc phosphazenes 300-303 were prepared by [2 + 2]-cycloaddition of phosphorus ylides 296-298 and R₅-nitriles (Scheme 121).³⁄₇ R₅-phosphazenes 300-303 can be used in the aza-Wittig reaction with aldehydes for the preparation of fluoroalkylated 2-azadienes.³⁄₇

![Scheme 121. Synthesis of R₅-phosphazenes 300-303.](image)

In accordance with an improved procedure, gaseous CF₃CN and CF₃CF₂CN were bubbled through a cooled (0 °C) solution of a phosphorus ylide 296 to afford the corresponding R₅-phosphazenes 300,301,304 (the E-isomers) in 61-90% yield.³⁄₇ Heating (E)-300,301,304 at 110 °C in toluene leads to their isomerization, producing the Z-isomers, (Z)-300,301,304, which were isolated in 98% yield (Table 12).³⁄₇
Table 12. Synthesis of R^f-phosphazenes 300,301,304

| Entry | R^f   | Product     | Yield, % |
|-------|-------|-------------|----------|
| 1     | CF_3  | (E)-300     | 90       |
| 2     | CF_3  | (Z)-300     | 98       |
| 5     | n-C_7F_{15} | (E)-301   | 83       |
| 6     | n-C_7F_{15} | (Z)-301   | 98       |
| 3     | C_2F_5 | (E)-304     | 61       |
| 4     | C_2F_5 | (Z)-304     | 98       |

β,β-Disubstituted enamine 305 reacted with CF_3CN at 40 °C to give 2-aza-1,3-pentadiene derivative 307 (75%). The authors noted that most likely, the reaction proceeds via the formation of 1-azetine intermediate 306 (Scheme 122).

Scheme 122. Reaction of β,β-disubstituted enamine 305 with CF_3CN.

The Diels-Alder cycloaddition of R^f-nitriles and 1,2-butadiene proceeds at 400 °C to give R^f-pyridines 309 in 97-99% yield (R^f = CF_3, C_2F_5, CF_3CF_2CF_2) and 12% yield (R^f = CClF_2) (Scheme 123).

Scheme 123. Diels-Alder cycloaddition of R^f-nitriles and 1,2-butadiene.
Scheme 124. Dissociation of ClCF₂CN N141 at 400 °C and formation of tetrafluoroethylene, and CF₂ addition product 310.

The Diels-Alder reaction of perfluorotriene 311 with CF₃CN at 400 °C gave 1,4,5,6,7,8-hexafluoro-3-(trifluoromethyl)isoquinoline (312) in 30.5 % yield. Some amounts of intermediate compounds 313 and 314 were also isolated (Scheme 125).

Scheme 125. Synthesis of 1,4,5,6,7,8-hexafluoro-3-(trifluoromethyl)isoquinoline (312).

Norbornadiene (315) reacts with trifluoroacetonitrile only at high temperatures (180–190 °C), and a long reaction time (40 h) was required to obtain CF₃-azatetracyclononene (316) as the [2+2+2]-cycloadduct, in 34% yield (Scheme 126).
Scheme 126. Cycloaddition of CF$_3$CN and norbornadiene.

The reaction of ynamine 317 and CF$_3$CN at 0 °C resulted in the formation of pyrimidine 318 ([2+2+2]-cycloaddition) (Scheme 127).\textsuperscript{123}

Scheme 127. [2+2+2]-Cycloaddition of ynamine 317 and CF$_3$CN.

The cycloaddition reaction of quadricyclane (319) and R$_F$-nitriles was studied.\textsuperscript{142} Nitriles, in general, are not active towards 319.\textsuperscript{143} However, it was found that R$_F$-nitriles have surprisingly high reactivity towards 319. In contrast to MeCN, which is totally inert towards quadricyclane (100 °C, 16 h), CF$_3$CN, C$_2$F$_5$CN, and n-C$_3$F$_7$CN rapidly react with 319 at elevated temperature producing exo-3-aza-4-perfluoroalkyltricyclo[4.2.1.0$^{2,5}$]non-3,7-dienes 320-322 (Scheme 128).\textsuperscript{142}

Scheme 128. Cycloaddition of quadricyclane (319) and R$_F$-nitriles.

The [4 + 2]-cycloaddition of azetes 323 and 324, and CF$_3$CN at 20 °C in either CH$_2$Cl$_2$ or CHCl$_3$, and the subsequent Dewar isomerization of bicyclic intermediates 325 resulted in isolation of CF$_3$-pyrimidines 326 and 327 in 71-91% yield (Scheme 129).\textsuperscript{144}
Scheme 129. [4 + 2] cycloaddition of azetes 323 and 324, and CF$_3$CN at 20 °C, and subsequent Dewar isomerization to CF$_3$-pyrimidines 326 and 327.

Trifluoroacetonitrile was used in a three-component reaction for the synthesis of 4-trifluoromethyl-$\Delta^3$-imidazolines 329. The reaction of an acyl halide with an $\alpha$-trimethylsilylimine generates an azomethine ylide 328, which then undergoes a 1,3-dipolar cycloaddition reaction with CF$_3$CN to afford 4-trifluoromethyl-$\Delta^3$-imidazolines 329. Such acylating agents benzoyl chloride, benzyl chloroformate, allyl chloroformate, and amino acid fluorides (AA-F) were used. The acid chlorides and chloroformates initiated the dipolar cycloadditions effectively at 55 °C, whereas the acid fluorides required temperatures around 75 °C. The Alloc and Cbz protecting groups are very effective in the cycloaddition and showed high stability to a wide range of conditions, including acid and strong base. Imidazolines 329 are readily hydrolyzed in MeOH or MeCN/H$_2$O in the presence of dilute HCl to afford N-protected phenyl glycine-derived CF$_3$-ketones 330 (Scheme 130).

Scheme 130. 1,3-Dipolar cycloaddition of intermediate azomethine ylide 328 and CF$_3$CN.

The reaction of imine 331 with BzCl and CF$_3$CN afforded a mixture of imidazoline 332 and acyclic enediamine-imine derivative 333. Imine 331 proved to be a fairly poor substrate for the cycloaddition reactions, as shown by the low yield of 332 (21%) and the tendency for 332 to undergo ring-opening to 333. The reaction of CbzCl with 331 did not produce the corresponding ring-opened compound 335, but the yield of desired imidazoline 334 was still low (33%) (Scheme 131).
Scheme 131. Reaction of imine 331 with CF₃CN in the presence of either BzCl or CbzCl.

In contrast to 331, imine 336 afforded 2-methyl-2-phenyl substituted imidazolines 337 and 338 in improved yield (57-54%), and with excellent regioselectivity. The cycloaddition reaction also tolerated the significant bulk from two germinal phenyl substituents of imine 339 and afforded a modest yield of imidazoline 340 (Scheme 132).

Scheme 132. Synthesis of CF₃-imidazolines 337, 338, and 340.

2,2,2-Trifluorodiazoethane (341) and CF₃CN reacted completely in two days to give nitrogen, recovered CF₃CN, and 2-(2,2,2-trifluoroethyl)-4,5-bistrifluoromethyl-1,2,3-triazole (342) (84%) (Scheme 133).
Scheme 133. Synthesis of triazole 342.

*N*-iminoypyridinium ylide (343) reacts with trifluoroacetonitrile (1,3-dipolar cycloaddition) giving 2-(trifluoromethyl)s-triazolo[1,5-a]pyridine (345) (Scheme 134).\(^{147}\) Compound 345 was isolated in 39% yield in 75-mol.% purity.\(^{147}\)

Scheme 134. Synthesis of 2-(trifluoromethyl)-s-triazolo[1,5-a]pyridine (345).

It was shown in 1973 that diazomethyltrimethylsilane (346) reacts with CF\(_3\)CN to give *N*-trimethylsilyl-4-trifluoromethyl-1,2,3-triazole, probably the 2-trimethylsilyl isomer 347.\(^{148}\) Cycloadduct 347 was readily hydrolyzed by aqueous EtOH or by atmospheric moisture to give 4-trifluoromethyl-1,2,3-triazole (348) (Scheme 135).\(^{148}\)

Scheme 135. Synthesis of 4-CF\(_3\)-1,2,3-triazoles 347 and 348.

The reactions of R^*CN with azides can be considered as 1,3-dipolar [3 + 2]-cycloadditions. Thus, sodio-5-trifluoromethyltetrazole (349) was synthesized in 75% yield through the reaction of CF\(_3\)CN with NaN\(_3\) in MeCN (the temperature of the reaction mixture rose spontaneously to 60 °C).\(^{149}\) Treatment of salt 349 with aqueous HCl resulted in analytically pure 5-trifluoromethyltetrazole (350) (Scheme 136).\(^{149}\)

Scheme 136. Synthesis of sodio-5-trifluoromethyltetrazole (349) and 5-trifluoromethyltetrazole (350).
Furthermore, besides the reaction of CF$_3$CN with NaN$_3$, the reactions of the CF$_3$CF$_2$CN and CF$_3$CF$_2$CF$_2$CN with NaN$_3$ in MeCN forming sodio-5-R$_F$-tetrazoles 351 and 352, were undertaken (Scheme 137).

$$
\text{ Scheme 137. Synthesis of sodio-5-R$_F$-tetrazoles 349, 351, and 352.}
$$

A similar approach for the synthesis of sodio-5-(trifluoromethyl)tetrazole 349 (40%) through bubbling CF$_3$CN into a solution of NaN$_3$ in MeCN at 25 °C was described.

The reaction of (O$_2$N)$_2$CFCN and O$_2$NCF$_2$CN with NaN$_3$ proceeds at ~20 °C, giving the corresponding R$_F$-sodio-tetrazoles 353 and 354 (80%), and is accompanied by practically no exothermic effect. Treatment of 353 and 354 with dry HCl in CH$_2$Cl$_2$ gave R$_F$-tetrazoles 355 and 356 (94.8-99%) (Scheme 138).

$$
\text{ Scheme 138. Synthesis of R$_F$-tetrazoles 355 and 356.}
$$

1,5-Disubstituted tetrazoles can also be synthesized from R$_F$-nitriles. Thus, reaction of fluorodinitroacetonitrile and difluoronitroacetonitrile with methyl azide in dry ether resulted in the corresponding R$_F$-tetrazoles 357 and 358, which were isolated in 48.2-34.8% yield (Scheme 139).

$$
\text{ Scheme 139. Synthesis of R$_F$-tetrazoles 357 and 358.}
$$

Tetrazole 359, a fluorine-containing estrone derivative, was prepared in 47% yield through the reaction of difluoronitrile N61 with NaN$_3$ (Scheme 140).
3.5. **R^f^-nitriles as active methylene compounds**

Fluoroacetonitrile and its α-monosubstituted derivatives are active methylene compounds, which can be used in various synthetic strategies for the preparation of fluorine-containing substances. Thus, the reaction of fluoroacetonitrile with ethyl formate in the presence of KOBu\textsuperscript{t} gave potassium (Z)-2-cyano-2-fluoroethenolate (360) (77\%) (Scheme 141),\textsuperscript{35} an attractive and readily available building-block for the synthesis of fluorinated heterocycles such as fluorinated pyrimidines and pyrazoles.\textsuperscript{151} The approach was expanded by using of various bases such as KOBu\textsuperscript{t}, NaOBu\textsuperscript{t}, NaOAm\textsuperscript{t}, NaHMDS, and methyl/ethyl formates, that allowed preparation of sodium and potassium (Z)-2-cyano-2-fluoroethenolates in 35-79\% yield. No target product was isolated when such bases as NaOMe, NaH, KOEt were used.\textsuperscript{35}

Scheme 141. Synthesis of potassium (Z)-2-cyano-2-fluoroethenolate (360).

The reaction of FCH\textsubscript{2}CN with diethylchlorophosphosphate at -78 °C, in the presence of LiN(TMS)\textsubscript{2}, and the subsequent treatment of the reaction mixture (intermediate anion 361) with aromatic aldehydes, gave 1-cyano-1-fluoroalkenes 362-368 in 45-82\% yield.\textsuperscript{152} Aliphatic aldehydes don’t allow preparation of 1-cyano-1-fluoroalkenes, producing complex mixtures (Table 13).\textsuperscript{152}

Table 13. Synthesis of α-fluoro-α,β-unsaturated nitriles 362-368\textsuperscript{152}

| Entry | Aldehyde | Product | Yield, % |
|-------|----------|---------|---------|
| 1     | ![Image](image1.png) | ![Image](image2.png) | 46      |
Table 13. Continued

| Entry | Aldehyde | Product | Yield, % |
|-------|----------|---------|----------|
| 2     | ![Image](image1) | ![Image](image2) | 45       |
| 3     | ![Image](image3) | ![Image](image4) | 52       |
| 4     | ![Image](image5) | ![Image](image6) | 62       |
| 5     | ![Image](image7) | ![Image](image8) | 82       |
| 6     | ![Image](image9) | ![Image](image10) | 51       |
| 7     | ![Image](image11) | ![Image](image12) | 45       |

The use of fluoroacetonitrile in the Horner–Wittig reaction allows preparation of α-fluoro acrylonitriles. The reaction of FCH$_2$CN with Ph$_2$P(O)Cl leads to the formation of nucleophilic anions 369, which then react with aldehydes and ketones to give α-fluoro-α,β-unsaturated nitriles 370, which were isolated in 31-73% yield (Scheme 142).

Scheme 142. Synthesis of α-fluoro-α,β-unsaturated nitriles 370.
The Wittig-Horner reaction of diethyl cyanofluoromethanephosphonate (N63), an α-fluorinated nitrile, with aldehydes and ketones yielded various α-fluoro-α,β-unsaturated nitriles 371-380 as Z:E mixtures in 30-58% yield (Table 14).\textsuperscript{64}

Table 14. Synthesis of α-fluoro-α,β-unsaturated nitriles 371-380\textsuperscript{64}

| Entry | Carbonyl compound | Product | Yield of product, % | Z:E |
|-------|-------------------|---------|---------------------|-----|
| 1     | PhCHO             | PhCH=CF CN (371) | 54                  | 1:2 |
| 2     | 3                  | 372     | 53                  | 2:3 |
| 3     | 4                  | 373     | 38                  | 2:3 |
| 4     | 5                  | 374     | 42                  | 1:2 |
| 5     | 6                  | 375     | 54                  | 1:2 |
| 6     | 7                  | 376     | 30                  | 7:3 |
| 7     | 8                  | 377     | 58                  | 1:1 |
| 8     | 9                  | 378     | 40                  | 1:1 |
| 9     | 10                | 379     | 46                  | 1:2 |

| 10    | PhCH\textsubscript{2}CHO | PhCH\textsubscript{2}CH=CF CN (380) | 50 | 3:2 |

Treatment of aldehyde 380 with 2-(O,O-diethylphosphono)-2-fluoroacetonitrile (N63) in the presence of NaH in DME gave α,β-unsaturated α-fluoronitrile 381 as a 1:1 mixture of the $E$ and $Z$ isomers, that was part of work on the preparation of a new fluoro-substituted HMG-COA reductase inhibitor (Scheme 143).\textsuperscript{153}
Scheme 143. Synthesis of \( \alpha,\beta \)-unsaturated \( \alpha \)-fluoronitrile 381.

\( \alpha \)-Fluoronitrile N11 was used as a building-block to synthesize various \( \alpha,\beta \)-unsaturated \( \alpha \)-fluoronitriles 382 in high yields and with good Z-stereoselectivity. The reaction of N11 with aliphatic, aromatic and heteroaromatic aldehydes in the presence of DBU as a base gave 382 in 59-98% yield (Scheme 144).

\[
\begin{align*}
\text{N11} & \quad \text{RCHO} \\
\text{DBU} & \quad 59-98\% \\
\text{382} & \quad \text{R = Alkyl, Aryl, Heteroaryl}
\end{align*}
\]

Scheme 144. Synthesis of \( \alpha,\beta \)-unsaturated \( \alpha \)-fluoronitriles 382.

Treatment of fluoroacetoniitrile (N2) with CS\(_2\) and Mel, and then LHMDS, yielded \( \alpha \)-fluoroacrylonitrile derivative 383 in 66% yield (Scheme 145).

\[
\begin{align*}
\text{FCH}_2\text{CN} & \quad 1. \text{CS}_2, \text{Mel} \\
& \quad 2. \text{LHMDS} \\
& \quad 66\% \\
\text{383} & \quad \text{MeS}^	ext{CN}
\end{align*}
\]

Scheme 145. Reaction of FCH\(_2\)CN with CS\(_2\) in the presence of Mel and LHMDS.

The reaction of dibromofluoroacetoniitrile (N150) with methacrolein was conducted in manner similar to that described for Cl\(_2\)FCCN (see paragraph 2.12, Scheme 45): the reaction in propionitrile at 110 °C, in the presence of CuCl as catalyst and Bu\(_3\)P/Et\(_3\)N as cocatalysts, resulted in the formation of functionalized \( \alpha \)-fluoronitrile 384 as a mixture of diastereomers. Attempts to purify crude 384 by distillation, instead, lead to the isolation of 2-bromo-3-fluoro-5-methylpyridine (385) in 11.7% yield (Scheme 146).
Scheme 146. Reaction of dibromofluoroacetonitrile (N150) with methacrolein in the presence of CuCl/Bu₃P/Et₃N.

No pyridine products were found during the distillation of the adducts formed from Cl₂FCCN N80 and methacrolein: all pyrolytic attempts at ring closure resulted in the formation of tars and multiple reaction products.³⁷

3.6. Heterocyclizations of 3-amino-2,2-difluoropropanenitriles with isocyanates and cyanoacetic acid

Reaction of 3-amino-2,2-difluoropropanenitriles N105 and N151 with isocyanates at 130 °C, and the subsequent treatment of intermediates 386 with either Et₃N or DBU in MeCN at rt yielded iminopyrimidones 387 in 78-99% yield. Intermediate substances 386 were also isolated (80-95%) and characterized (Table 15).¹⁵⁶

Table 15. Synthesis of iminopyrimidones 387¹⁵⁶

| Entry | R¹ | R² | R³ | 386 Yield of 386, % | 387 Base | Yield of 387, % |
|-------|----|----|----|-------------------|---------|----------------|
| 1     | Ph | Me | Ph | 386a 95          | 387a Et₃N | 95             |
| 2     | Ph | Me | 4-ClC₆H₄ | 386b 95 | 387b Et₃N | 97             |
| 3     | 2-thienyl | Bn | Ph | 386c 83 | 387c Et₃N | 98             |
| 4     | 2-thienyl | Bn | 4-ClC₆H₄ | 386d 80 | 387d Et₃N | 99             |
| 5     | Ph | Me | Pr | 386e 93 | 387e DBU | 78             |

Pyrimido[1,6-a]benzimidazolones 391 were synthesized in 75-81% yields from 3-amino-2,2-difluoropropanenitriles N105, N151-154 and o-iodophenylisocyanate, and intermediate substances 388 were also isolated (67-96%) and characterized (Table 16).¹⁵⁶
**Table 16. Synthesis of pyrimido[1,6-\(a\)]benzimidazolones 391**

Fluorinated 4-amino-5,6-dihydropyridin-2(1H)-ones 392 (16-97\%) were synthesized from \(\alpha,\alpha\)-difluoronitriles N105, N152, N154 and N155 and cyanoacetic acid in the presence of EDC·HCl. The plausible mechanism involves the formation intermediates 393 formed in the acylation step, which then undergo the ring closure (the Thorpe—Ziegler reaction) to give 392 (Table 17).
Table 17. Synthesis of fluorinated 4-amino-5,6-dihydropyridin-2(1H)-ones 392

| Entry | R¹  | R²   | Product 392 | Yield of 392, % |
|-------|-----|------|-------------|-----------------|
| 1     | Ph  | Me   | 392a        | 95              |
| 2     | 2-furyl | Me | 392b       | 97              |
| 3     | 4-MeOC₆H₄ | Et | 392c       | 93              |
| 4     | 2-thienyl | Bn | 392d       | 43              |
| 5     | 2-furyl | cyclohexyl | 392e   | 16              |

3.7. Reduction
It was shown, that CF₃CN can be reduced to 2,2,2-trifluoroethylamine (394) (50-80%) by hydrogenation in the presence of PtO₂ (Scheme 147).²⁹

Scheme 147. Synthesis of 2,2,2-trifluoroethylamine.

2,2-Difluoroethylamine hydrochloride (396) (91.1%) was prepared in 69% overall yield via the reduction of CHF₂CN with H₂/Pd in Ac₂O/THF at ~20 °C, and the subsequent hydrolysis of intermediate amide 395 with 32% HCl at 90 °C (Scheme 148).¹⁵⁸ Other acylating agents and reductants can also be used for the preparation of 396.¹⁵⁸
Scheme 148. Preparation of 2,2-difluoroethylamine hydrochloride (396).

The α-chlorine atom can selectively be removed from a molecule of α-chloro-α-fluoronitriles by reduction. Thus, the reduction of α-fluoronitrile (N82) with 5% Cd/Hg α-dechlorinated α-fluoronitrile N156, which was hydrolyzed with formic acid to afford functionalized α-fluoronitriles N157 in 65% yield.\(^{37}\) Cyclization of N157 under the action of HCl in MeCN at 180 °C gave 2-chloro-3-fluoro-5-methylpyridine (397) in 44% yield (Scheme 149).\(^{37}\)

Scheme 149. Synthesis of functionalized α-fluoronitriles N156 and N157, and fluoropyridine 397.

3.8. Other reactions

β-Fluorinated nitriles N13 and N39 undergo the nitrile-ketenimine tautomerism, and they were methylated with diazomethane to give trifluoromethylated N-methylketenimines 399 and 400 in 14 and 56% yields, respectively (Scheme 150).\(^{58}\)

Scheme 150. Nitrile-ketenimine tautomerism and synthesis of N-methylketenimines 399 and 400.

Treatment of bis(triphenylphosphine)platinum trans-stilbene with excess of CF₃CN gives the complex bis(triphenylphosphine)platinum-CF₃CN 401.\(^{159}\) The proposed structure is based on the 56.4 MHz \(^{19}\)F NMR
spectrum and an intense IR absorption of 1734 cm$^{-1}$ in the region normally assigned to the C=N stretching frequency.$^{159}$ Another product, isolated from the reaction of CF$_3$CN and Pt(PPh$_3$)$_4$, for which chemical analysis shows the molecular formula (PPh$_3$)$_2$Pt(CF$_3$CX)$_2$N $^{402}$, was subjected to a single-crystal X-ray diffraction structure determination (Figure 1).$^{159}$

\[ \text{Figure 1. Formation of platinum complexes 401 and 402.} \]

Kinetics and mechanism of free-radical addition of CF$_3$CN to ethylene at 350-450 $^\circ$C were explored, and such products as 4,4,4-trifluorobutyronitrile, 6,6,6-trifluorohexanenitrile, perfluoroethane, 1,1,1,4,4,4-hexafluorobutane, and 1,1,1,6,6,6-hexafluorohexane were detected.$^{160,161}$

4. Conclusions

Thus, fluoroalkyl cyanides, attractive electrophilic, enophilic, and dienophilic building-blocks, can be synthesized via a large variety of synthetic methods, that makes them both synthetically valuable and readily available reagents. R$^2$-Nitriles are versatile reagents: They can react with electrophiles at the C≡N group to produce various unusual reactive structures, they can play role of active methylene compounds, and they can be used as highly reactive building-blocks in cyclizations for the syntheses of fluorine-containing heterocyclic compounds. Fluoroalkyl cyanides are important reactants in medicinal chemistry for the design, development, and synthesis of pharmaceutical drugs.

5. Abbreviations

| Abbreviation | Full Form                        |
|--------------|---------------------------------|
| Alloc        | allyloxycarbonyl                |
| aq           | aqueous                         |
| Cbz          | benzyloxycarbonyl               |
| DAST         | diethylaminosulfur trifluoride  |
| DBU          | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DEG          | diethylene glycol               |
| DME          | 1,2-dimethoxyethane             |
| DMF          | dimethylformamide               |
| DMSO         | dimethyl sulfoxide              |
| EDC          | 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| HMDS         | hexamethyldisilazane            |
| HMPA         | hexamethylphosphoramidide       |
| LDA          | lithium diisopropylamide        |
LiHMDS lithium bis(trimethylsilyl)amide
liq liquid
Menth menthyl
NFSI N-fluorobenzenesulphonimide
PPA polyphosphoric acid
R\textsuperscript{F} fluoroalkyl
rt room temperature
TFA trifluoroacetic acid
THF tetrahydrofuran
TM tautomerism
TMS trimethylsilyl
TMSCN trimethylsilyl cyanide

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