Fluorinated Triazines

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Contents

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Abstract In this chapter data on structure, synthetic routes, reactivity of derivatives of 1,2,3-triazines, 1,2,4-triazines and 1,3,5-triazines – bearing one or several fluorine atoms in heterocyclic ring as well as trifluoromethyl substituted triazines are considered and analyzed, and also their certain representatives are discussed. The bibliography – 119 references.

Keywords Fluorine • Trifluoromethyl group • Triazine • NMR spectroscopy • Antiviral activity • Dyes

1 Introduction

A growing interest to fluorinated derivatives of triazines which is observed for the recent two decades has undoubtedly stimulated the development of new synthetic methods, as well as studying of their reactivity and elucidation of areas of their plausible applications.

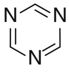
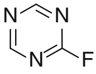
2 Structure

In this section the data of theoretical studies reflecting the effects of fluorine atom(s) on geometrical characteristics of fluorine-containing triazines will be discussed. Selected examples of the X-ray crystallography analysis of 1,3,5-triazines, 1,2,4-triazines and 1,2,3-triazines as well as the data of ^{19}F NMR spectroscopy elucidations will be considered.

2.1 Quantum-Chemical Calculations

The effects of incorporating of a fluorine atom in the position 2 of 1,3,5-triazine ring have been estimated by *ab initio gradient* method [1]. According to the data of quantum chemical calculations (Table 1), the angle of $N^1C^2N^3$ increases of 1.6°, the bonds C^2-N^1 and C^2-N^3 become shorter of 0.0017 nm. It should be noted that the C-F bond in 2-fluoro-1,3,5-triazine is shortest one relative to 2-fluoropyridine (the

Table 1 Characteristics of 1,3,5-triazine and 2-monofluoro analogue

Parameter		
Bond length, nm		
$N^1–C^2$, $N^3–C^2$	0.1332	0.1315
$N^3–C^4$	0.1332	0.1332
$C^4–N^5$	0.1332	0.1332
$C^2–X^2$	0.1067	0.1332
$C^4–H^4$	0.1067	0.1066
$C^6–H^6$	0.1067	0.1066
Valency angles		
$C^6N^1C^2$	116.1	115.5
$N^1C^2N^3$	***123.9***	***125.5***
$N^3C^4N^5$	123.9	123.7
$C^4N^5C^6$	116.1	116.0
$N^1C^2X^2$	118.1	119.0
$N^3C^4H^4$	118.1	117.8
Dipolar moment	0	2.28

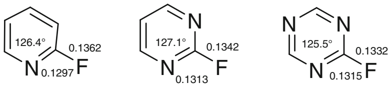


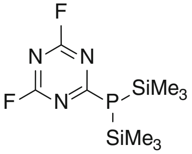
Fig. 1 Bond lengths (nm) and angles for 2-fluoropyridine, 2-fluoropyrimidine and 2-fluoro-1,3,5-triazine

difference is –0.003 nm) and 2-fluoropyrimidine (–0.001 nm) (Fig. 1). Calculations using HF//6-31G*//6-31G* gave following values of the N-F bond distances in 1-fluoro-2,4,6-trichloro-*s*-triazinium hexafluoroarsenate and 1-fluoro-*s*-triazinium hexafluoroarsenate: 0.1314 nm and 0.1317 nm respectively [2].

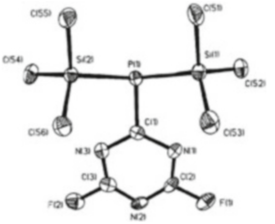
2.2 X-ray Crystallography Analysis Data

Research of fluorinated derivatives of triazine by the X-ray method has fragmentary character. Fluorinated 1,3,5-triazines are most in detail considered. The X-ray data for 2,4-difluoro-6-bis(trimethylsilylphosphino)-1,3,5-triazine (Fig. 2) have been obtained [3]. The $P(CN)_3$ fragment of the molecule is practically planar, however the angles in the 1,3,5-triazine ring proved to differ considerably from those of the correct hexagon figure. The $C^1–N^1–C^2$ angle is 112.3°, while the opposite angle $N^2–C^3–N^3$ has a much higher value of 132.0°. The C-N bond lengths have value which are typical for the corresponding double bond (0.131–0.135 nm), whereas C-P bond is significantly longer (0.181 nm), but keeps within an interval of typically C-P bond.

Also fluorinated anionic triazine systems with TAS^+ $[(Me_2N)_3S^+]$ cation have been studied by the X-ray crystallography (Figs. 3, 4, 5 and 6) [4]. It has been shown that values of the $C^1–N^1$ and $C^1–N^3$ bonds in the anion $C_3N_3F_4^-$ correspond to those

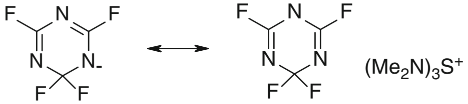


Bond lengths (nm):
C^1-N^1 0.131(2), C^1-N^3 0.136(2),
C^1-P^1 0.181(1), C^2-N^1 0.130(2),
C^2-N^2 0.132(2), C^2-F^1 0.133(1),
C^3-N^2 0.131(1), C^3-N^3 0.130(2),
C^3-F^2 0.134(2), P^1-Si^1 0.2256(5),
P^1-Si^2 0.272(5), Si^1-C^{51} 0.186(2),
Si^1-C^{52} 0.186(2), Si^1-C^{53} 0.186(1),
Si^2-C^{54} 0.186(2), Si^2-C^{55} 0.186(2),
Si^2-C^{56} 0.186(2).



Valency angles:
N^1-C^1-N^3 123.4(8), N^1-C^1-P^1 118.4(8),
N^3-C^1-P^1 117.1(6), N^1-C^2-N^2 130.7(8),
N^2-C^3-N^3 130.5(8), C^1-N^1-C^2 113.1(7),
S-^{1}-P^1-Si^2 112.6(3), C^1-P^1-Si^2 101.1(4),
C^1-P^1-Si^1 101.9(4), C^1-N^3-C^3 112.6(7),
C^2-N^2-C^3 109.4(8).

Fig. 2 X-ray data for 2,4-difluoro-6-bis(trimethylsilylphosphino)-1,3,5-triazine (Reproduced with permission of ACS [3])



Bond lengths (nm):
C^1-F^1 0.1400(4), C^1-F^2 0.1383(4),
C^1-N^1 0.1403(4), C^1-N^3 0.1400(4),
N^1-C^2 0.1277(4), N^3-C^3 0.1279(4),
C^2-N^2 0.1329(4), N^2-C^3 0.1319(4),
C^2-F 0.1345(3), C^3-F 0.1348(3).
Valency angles: N^1-C^1-N^3 120.4(3),
N^1-C^2-N^2 132.0(3), F^1-C^1-F^2 101.1(2)

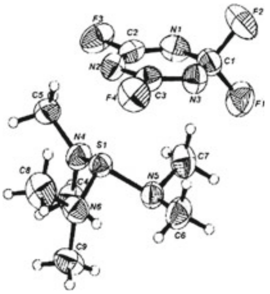
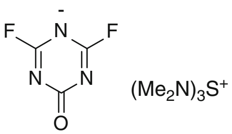


Fig. 3 X-ray data for TAS⁺ $C_3N_3F_4^-$ (Reproduced with permission of RCS [4])



Bond lengths (nm):
C^1-O 0.1225(4), C^1-N^1 0.1390(4),
C^1-N^3 0.1391(5), N^1-C^2 0.1288(5),
N^3-C^3 0.1281(5), C^2-N^2 0.1310(6),
N^2-C^3 0.1322(6), C^2-F 0.1350(5),
C^3-F 0.1342(5).
Valency angles: N^1-C^1-N^3 119.4(3),
N^1-C^2-N^2 132.1(4).

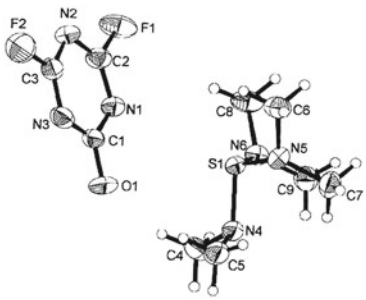
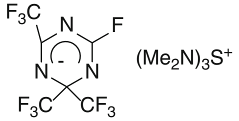


Fig. 4 X-ray data for PCA TAS⁺ $C_3N_3F_2O^-$ (With permission of RCS [4])



Bond lengths (nm):
C^1-N^1 0.1444(6), N^1-C^3 0.1263(7)
N^2-C^3 0.1332(8), C^1-C^2 0.1536(5),
C^4-C^5 0.1458(8).
Angle N^1-C^3-N^3 118.3(4),
sum of angles 720.3.

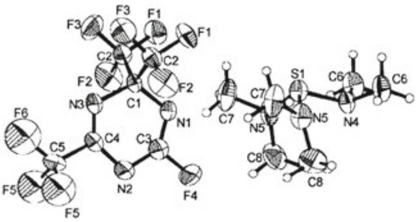
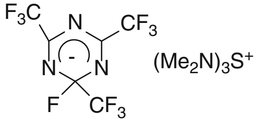


Fig. 5 X-ray data for TAS$^+$ $C_3N_3F(CF_3)_3^-$ (Reproduced with permission of RCS [4])



Bond lengths (nm):

C^1-N^1 0.1456(4), N^1-C^3 0.1302(4),
N^2-C^3 0.1334(4), C^1-C^2 0.1526(4),
C^5-C^6 0.1514(4).
Angle N^1-C^3-N^3 117.0(2),
sum of angles 716.7°.

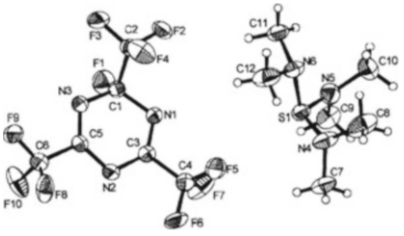
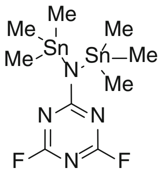


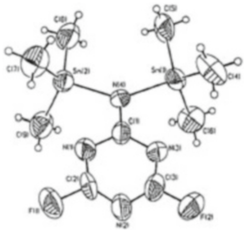
Fig. 6 X-ray data for TAS$^+$ $C_3N_3F(CF_3)_3^-$ (Reproduced with permission of RCS [4])

of the ordinary bond, the N^1–C^2 and C^3–N^3 bonds are double, while the C^2–N^2 and N^2–C^3 bonds proved to have intermediate values between ordinary and double bonds. The ring C_3N_3 fragment of compound TAS$^+$ $C_3N_3F_4^-$ is a planar one with the C^1 carbon atom to be in a tetrahedral configuration.

X-ray data for 2-tris(trimethylstannyl)amino-4,6-difluoro-1,3,5-triazine (Fig. 7) show that the triazine ring is a little distorted, the molecule is nearly planar with the exception of methyl groups. The maximum deviation from the plane is exhibited by tin atoms (0.009 nm). The enlarged angle N^2–C^3–N^3 (130.0°) is resisted by the angle C^2–N^1–C^1 (114.7°). The C-N bond attached to the triazine ring is unusually small and its length is very close to values of three other C-N bonds of the ring, thus indicating at a considerable π-linkage of the ring with the exocyclic nitrogen atom [5].

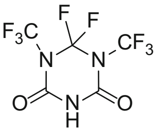
The N-F bond length (0.11 nm) in 1-fluoro-2,4,6-trichloro-*s*-triazine hexafluoroarsenate is shorter than its calculated value of 0.0214 nm [2]. Also perfluorinated hexahydro-1,3,5-triazin-2,6-dione has been studied by X-ray crystallography method (Fig. 8) [6].

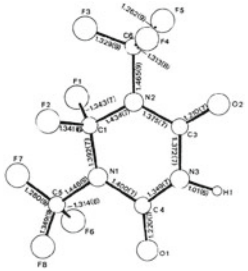




Bond lengths (nm):
N^4-C^1 0.1333(16), C^1-N^1 0.1366(16),
N^1-C^2 0.1297(18), C^2-N^2 0.1277(20),
N^2-C^3 0.1318(20), C^3-N^3 0.1311(19),
N^3-C^1 0.1356(16).
Valency angles: N^3-C^1-N^4 120.9(11),
N^4-C^1-N^1 118.8(11), C^1-N^1-C^2 114.7(11),
N^1-C^2-N^2 131.2(12), C^2-N^2-C^3 109.2(11),
N^2-C^3-N^3 130.0(12), C^3-N^3-C^1 144.3(11).

Fig. 7 X-ray data for 2-*tris*(trimethylstannyl)amino-4,6-difluoro-1,3,5-triazine (Reproduced with permission of ACS [5])





Valency angles: N^1-C^1-N^2 113.0(5),
C^1-N^2-C^3 124.3(5), N^2-C^3-N^3 115.4(5),
C^3-N^3-C^4 125.7(5), N^3-C^4-N^1 115.3(5),
C^4-N^1-C^1 125.1(5), F^1-C^1-F^2 104.9(4),
F^8-C^5-F^6 107.6(6), C^8-C^5-F^7 110.2(6),
F^6-C^5-F^8 106.3(6), F^5-F^6-F^4 108.7(6),
F^5-C^6-F^3 107.6(6), F^4-C^6-F^3 108.2(6).

Fig. 8 X-ray data for perfluorinated hexahydrotriazindione (Reproduced with permission of Elsevier [6])

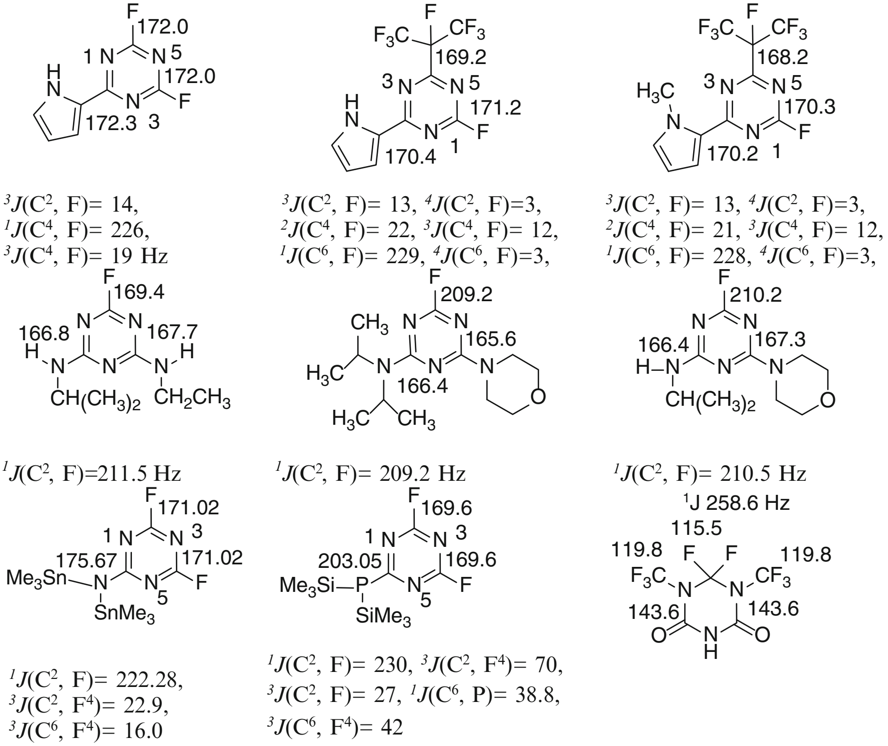
2.3 NMR Spectroscopy

Existence of three nitrogen atoms in a ring and such substituents as fluorine atoms in molecules of considered group of compounds does the most informative for the analysis of structure and properties NMR ^{13}C and ^{19}F spectroscopy.

2.3.1 NMR ^{13}C Spectroscopy

The data on NMR ^{13}C spectroscopy of 6-substituted fluorinated 1,3,5-triazines have been analyzed [3, 5, 7, 8]. Replacement of fluorine atom by $CF(CF_3)_2$ group leads to upfield shift of signals of triazine carbons in NMR ^{13}C spectra.

NMR ^{13}C spectra of perfluorinated hexahydrotriazinedione have been also studied (Scheme 1) [6].



$^3J(C^2, F)$= 14, $^1J(C^4, F)$= 226, $^3J(C^4, F)$= 19 Hz

$^3J(C^2, F)$= 13, $^4J(C^2, F)$=3, $^2J(C^4, F)$= 22, $^3J(C^4, F)$= 12, $^1J(C^6, F)$= 229, $^4J(C^6, F)$=3,

$^3J(C^2, F)$= 13, $^4J(C^2, F)$=3, $^2J(C^4, F)$= 21, $^3J(C^4, F)$= 12, $^1J(C^6, F)$= 228, $^4J(C^6, F)$=3,

$^1J(C^2, F)$=211.5 Hz

$^1J(C^2, F)$= 209.2 Hz

$^1J(C^2, F)$= 210.5 Hz

$^1J(C^2, F)$= 222.28, $^3J(C^2, F^4)$= 22.9, $^3J(C^6, F^4)$= 16.0

$^1J(C^2, F)$= 230, $^3J(C^2, F^4)$= 70, $^3J(C^2, F)$= 27, $^1J(C^6, P)$= 38.8, $^3J(C^6, F^4)$= 42

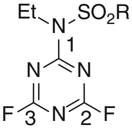
Scheme 1 NMR ^{13}C spectra data of fluorinated triazines

Cyclic carbons with fluorine atom in NMR ^{13}C spectra of boronfluoride salt of 2,4-difluoro-6-(1,3-diisopropyl-4,5-dimethylimidazolyl-2)-1,3,5-triazine are fixed in the form of a multiplet at 170.6–172.9 ppm [9]. NMR ^{13}C spectra of difluorosulphonamido-1,3,5-triazines in THF-d_8 at different temperatures (Table 2) reveal that at the room temperature C^2 and C^3 atoms are equivalent, and at low temperatures rotation of the substituent round exocyclic C-N bond slows down so that C^2 and C^3 atoms become magnetically nonequivalent [10].

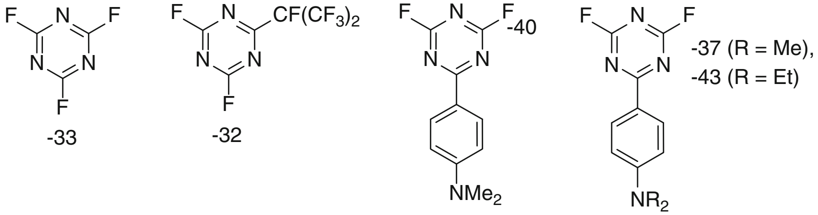
2.3.2 ^{19}F NMR Spectroscopy

The ^{19}F NMR spectra of a number of fluorinated 1,3,5-triazines have been reported (solvent $CDCl_3$), the chemical shifts of fluorine are observed at -32-(-42) ppm [8]. As the information about spectra of fluorine-containing diazines in the same solvent is absent, it is difficult to compare ^{19}F NMR spectra of fluorotriazines and fluorodiazines (Scheme 2).

Table 2 NMR ^{13}C data of difluorosulphonamido-1,3,5-triazines in THF-d_8 at different temperatures

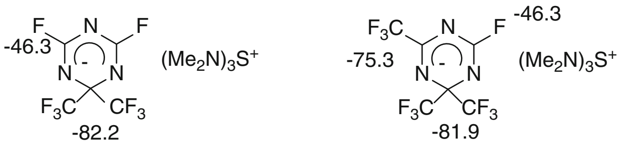


R	T, °C	Chemical shift of C^1	Chemical shift of C^2 and C^3
C_8F_{17}	2	170.6 t	172.4 dd
	−60	170.5 t	172.2 dd
C_8H_{17}	20	170.3 t	172.0 dd
	−50	170.0 t	173 br, 170 br
	−90	170.0 t	171.2 dd, 172.1 dd
$C_6H_4CH_3$	24	169.3 t	171.8 dd
	−60	168.9 t	173 br, 170 br
	−90	168.8 t	171.0 dd, 171.9 dd



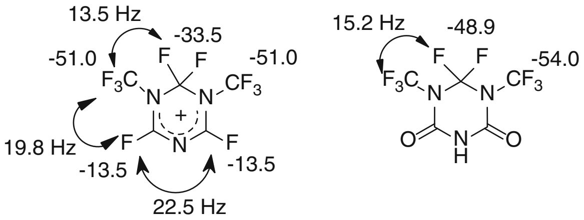
Scheme 2 Chemical shifts in ^{19}F NMR spectra of fluorinated 1,3,5-triazines

The NMR ^{19}F spectra of the salts consisting of the anionic fluorine-containing triazine systems and TAS$^+$ [$(Me_2N)_3S^+$] as the cation have been elucidated, the chemical shifts of aromatic fluorine are equal −46.3 ppm (Scheme 3) [4]:



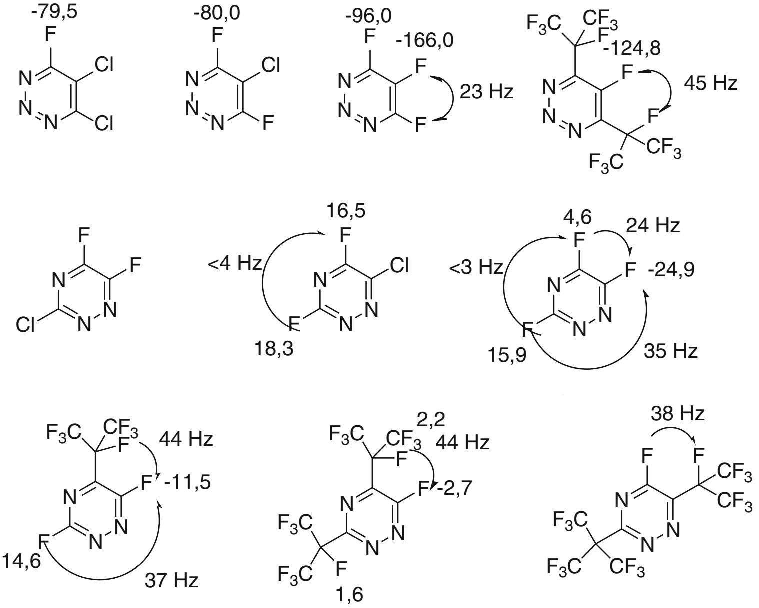
Scheme 3 The NMR ^{19}F spectra data of the anionic fluorine-containing triazine systems and TAS$^+$

The NMR ^{19}F spectra data for the delocalized 1,3,5-triazinium cation which is formed on treatment of 3,5-trifluoromethyl-2,4,4,6,6-pentafluoro-3,4,5,6-tetrahydro-1,3,5-triazine with SbF_5 have been presented, the chemical shifts of aromatic fluorine are −13.5 ppm (Scheme 4) [6].



Scheme 4 The NMR ^{19}F spectra data for the delocalized 1,3,5-triazinium cation

The data of ^{19}F NMR spectroscopy show that chemical shifts of fluorine atoms attached to the ring in 1,2,3-triazines are varied greatly and lay in range from −79.5 to −166.0 ppm [11]. The data on ^{19}F NMR spectra of fluorinated 1,2,4-triazines have recently been presented and discussed [12]. Coupling constants $^{5}J_{F(3),F(6)}$ lay in range from 35 to 37 Hz, constant $^{3}J_{F(5),F(6)}$ proved to be 24 Hz, whereas the $^{4}J_{F(3),F(5)}$ has smallest value (<4 Hz) (Scheme 5).



Scheme 5 Chemical shifts and coupling constants in ^{19}F NMR spectra of fluorotriazines

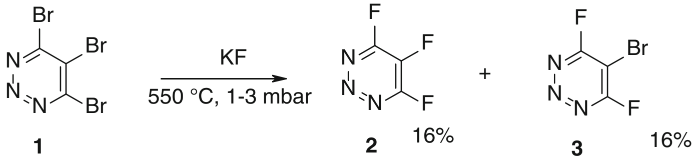
3 Synthetic Methods

One of the most common synthetic approach to 1,2,3-, 1,2,4- and 1,3,5-triazines, bearing fluorine atoms as substituents in the ring, consists of the nucleophilic displacement of chlorine or bromine atoms with the fluoride anion in the corresponding haloderivatives, a direct fluorination, the Shimman reaction in addition to another synthetic strategies based on condensations and ring transformations.

3.1 Synthesis of Fluorine-Containing 1,2,3-Triazines

3.1.1 Nucleophilic Displacement of Bromine or Chlorine Atoms with the Fluoride Anion

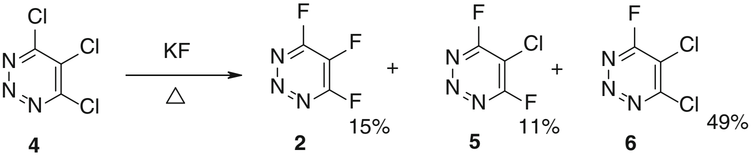
The displacement of bromine or chlorine atoms in heteroaromatic compounds is certainly one of the most effective synthetic methods leading to fluorinated heterocyclic compounds [13]. For instance, heating 4,5,6-tribromo-1,2,3-triazine **1** with dry potassium fluoride at 550 °C in vacuum results in the formation of a mixture of 4,5,6-trifluoro-1,2,3-triazine **2** and 5-bromo-4,6-difluoro-1,2,3-triazine **3** in the ratio 1:1 (Scheme 6) [14].



Scheme 6 Nucleophilic displacement of bromine atoms with the fluoride anion

The reaction of 4,5,6-trichloro-1,2,3-triazine **4** with potassium fluoride at an elevated temperatures provides fully substituted 4,5,6-trifluoro-1,2,3-triazine **2** in addition to compounds **5** and **6** with partial displacement of chlorine atoms (Scheme 7) [11]. It is clear that yields of fluorinated products depend on the reaction conditions (Table 3) [11]. At temperatures of 150–200 °C replacement of one or two chlorine atoms take place. The polyfluorinated 1,2,3-triazines **2, 5** were obtained when using two-step process in 55–69 % yields.

Interaction of 4,5,6-trichloro-1,2,3-triazine **4** with hexafluoropropene in the presence of potassium and cesium fluorides leads to the formation of

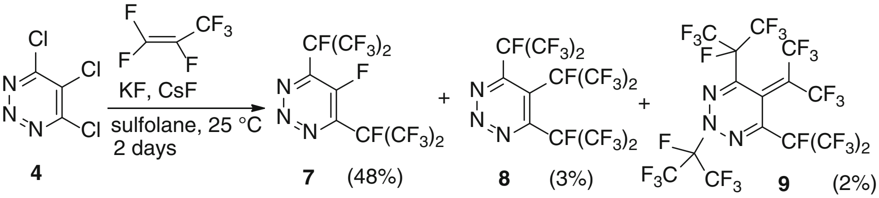


Scheme 7 The reaction of 4,5,6-trichloro-1,2,3-triazine **4** with KF

Table 3 Fluorination of 4,5,6-trichloro-1,2,3-triazine [11]

Reaction conditions		Yields, %		
	Temperature	**2**	**5**	**6**
KF, sealed tube	150 °C	–	11	49
10^{-2} mm, 18 h	180 °C	–	58	9
	200 °C	–	37	0
KF, vacuum	500 °C (1 cycle)	3	40	47
Transfer 10^{-2} mm	500 °C (4 cycles)	18	65	–
	(a) 500 °C (b) 600 °C	69	15	–
	(a) 450 °C (b) 700 °C	55	4	–
	(a) 450 °C (b) 600 °C	65	18	–

4,6-di-(perfluoroisopropyl)-5-fluoro-1,2,3-triazine **7** in addition to small quantities of polyfluorinated alkyl-1,2,3-triazines **8** and **9** (Scheme 8) [11, 15]. Trifluoromethyl substituted 1,2,3-triazines are still unknown compounds.



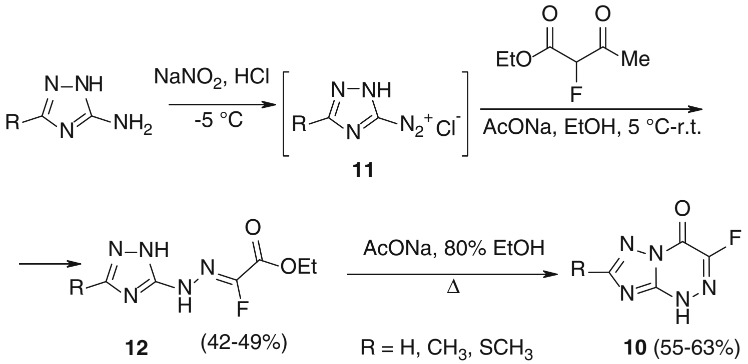
Scheme 8 Interaction of **4** with hexafluoropropene in the presence of KF and CsF

3.2 Synthesis of Fluorine-Containing 1,2,4-Triazines

Fluorinated 1,2,4-triazines can be obtained by means of several synthetic approaches: the formation of 1,2,4-triazine ring through cyclocondensations of fluorine-containing synthones, a direct fluorination of the ring, replacement of chlorine atoms in chlorotriazines with the fluoride anion and other methods.

3.2.1 Cyclocondensation Reactions

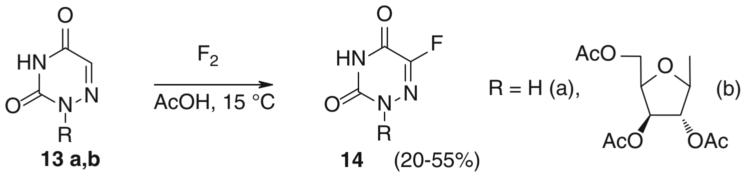
The synthesis of azoloannelated fluoro-1,2,4-triazines – 2-R-6-fluoro-1,2,4-triazolo[5,1-*c*][1,2,4]triazin-7(4H)-ones **10** has been recently described [16]. The coupling of 1,2,4-triazolyl-5-diazonium salts **11** with ethyl 2-fluoroacetate and the accompanied deacetylation leads to the formation of hydrazones **12** followed by cyclization on heating in aqueous alcohol in the presence of sodium acetate into the target fluoro compounds **10** (Scheme 9).



Scheme 9 Synthesis of triazolotriazin-7(4H)-ones **10**

3.2.2 Direct Fluorination Reactions

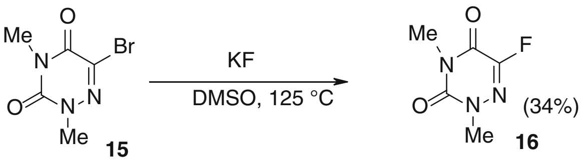
A rare example of the incorporation of a fluorine atom into azaaromatic compounds is the direct fluorination reaction of 6-azauracyl **13a** and 2-(2,3,5-tri-O-acetyl-β-D-ribofuranozyl-1,2,4-triazin)-3,5(2H,4H)-dione **13b** which takes place on passing of fluorine through a solution of azauracils **13a,b** in acetic acid, thus giving 6-fluoro-1,2,4-triazin-3,5(2H,4H)-diones **14** in 20–55 % yields (Scheme 10) [17, 18].



Scheme 10 Direct fluorination reactions

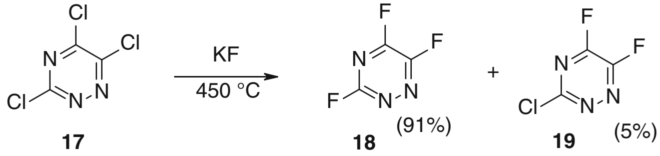
3.2.3 Nucleophilic Displacement of Bromine or Chlorine Atoms with the Fluoride Ion

The reaction of bromo or chloro derivatives of triazines with the fluoride ion is one of the main methods for the synthesis of fluorinated 1,2,4-triazines [13]. For instance, 1,3-dimetyl-5-fluoro-6-azauracyl **16** was obtained by reacting dry potassium fluoride with the corresponding bromo precursor **15** (Scheme 11) [19].



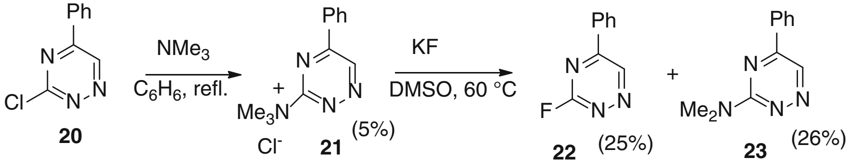
Scheme 11 Synthesis of 1,3-dimetyl-5-fluoro-6-azauracyl **16**

Another example illustrating utility of this approach is displacement of chlorine atoms in 3,5,6-trichloro-1,2,4-triazine which does occur in a melt of compound **17** with dry KF (Scheme 12) [20]. The conversion degree depends on the reaction conditions: at 450 °C the dominant product of the reaction proved to be 3,5,6-trifluoro-1,2,4-triazine **18**, while 3-chloro-5,6-difluoro-1,2,4-triazine **19** was isolated as a minor product.



Scheme 12 Displacement of chlorine atoms in 3,5,6-trichloro-1,2,4-triazine

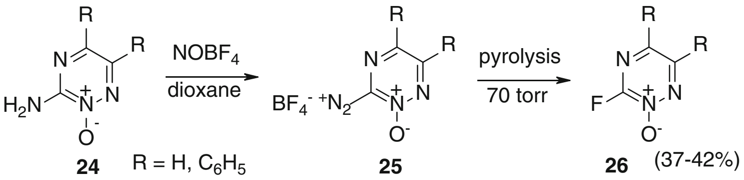
In order to obtain 3-fluoro-5-phenyl-1,2,4-triazine **22** from the corresponding 3-chloro derivative **20** the chlorine atom has to be displaced first with the trimethylammonium fragment (compound **21**), which undergoes easily the fluorination reaction by action of potassium fluoride to give 3-fluoro-1,2,4-triazine **22** in addition to 3-dimethylamino-5-phenyl-1,2,4-triazine **23** [21] (Scheme 13).



Scheme 13 Reaction of compound **21** with KF

3.2.4 The Baltz-Schiemann Reaction

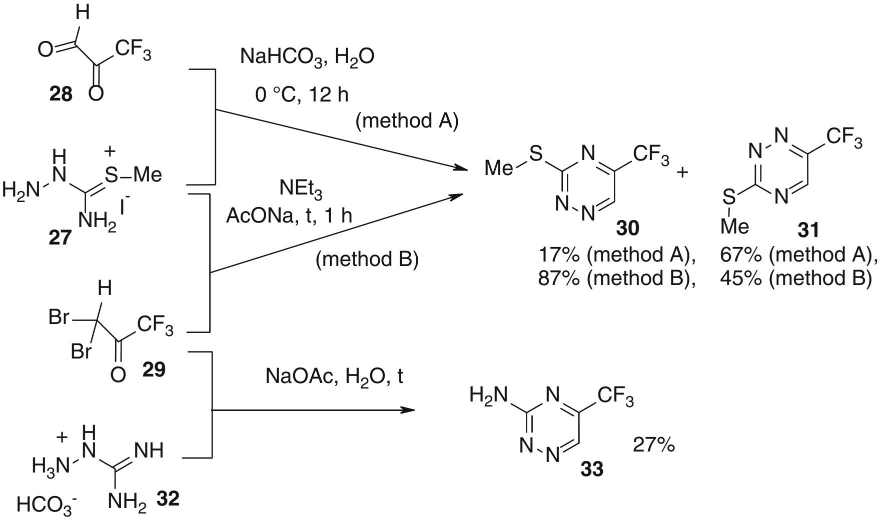
3-Fluoro-1,2,4-triazin-2-oxides **26** were obtained through diazotization of the corresponding amino derivatives **24** followed by thermolysis of the resulting diazonium tetrafluoroborates **25** (Scheme 14). It should be noted the salts **25** have been isolated first as rather stable heterocyclic diazonium species [22].



Scheme 14 The Baltz-Schiemann reaction

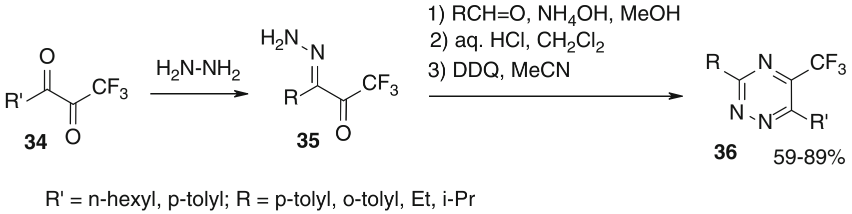
Two main synthetic approaches to trifluoromethyl substituted 1,2,4-triazines are known. They are cyclocondensation process based on (trifluoromethyl)carbonyl derivatives and transformation of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine ring.

A synthesis of 3-methylthio-5-trifluoromethyl-1,2,4-triazine **30** was described using dibromotrifluoroaceton **3** and S-methylthiosemicarbazide **27** as starting materials (Scheme 15) [23]. The synthesis of 3-methylthio-6-trifluoromethyl-1,2,4-triazine **31** was achieved by using trifluoropyruvaldehyde **28** and S-methylthiosemicarbazide **27** as starting materials (Scheme 15) [24]. 3-Aminotriazine **33** was prepared by the condensation of aminoguanidine **32** with dibromoketone **29**, this condensation was non-selective, and 6-trifluoromethyl-isomer as by-product was formed (Scheme 15) [25].



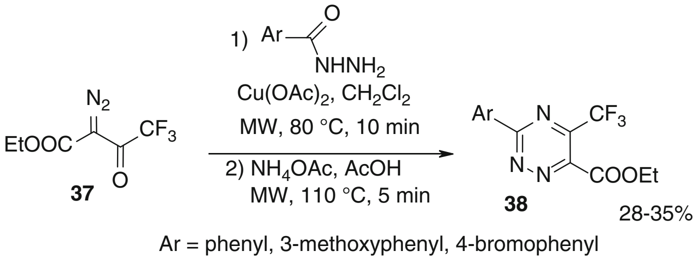
Scheme 15 Synthetic approaches to trifluoromethyl substituted 1,2,4-triazines

3-Hydrazono-1,1,1-trifluoroalkan-2-ones **35** prepared from 1,1,1-trifiuoroalkane-2,3-diones **34** reacted with several aldehydes in the presence of aqueous NH_4OH to afford 5-trifluoromethyl-2,3-dihydro-1,2,4-triazines, of which oxidation gave 5-trifluoromethyl-1,2,4-triazines **36** (Scheme 16) [26].



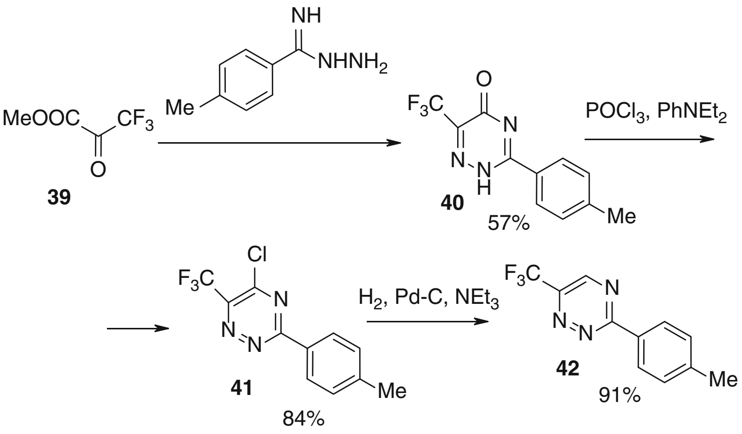
Scheme 16 Synthesis of 5-trifluoromethyl-1,2,4-triazines **36**

Microwave assisted reaction of 2-diazo-4,4,4-trifluoro-3-oxobutanoate **37** with aryl hydrazides in the presence of copper(II)acetate, followed by reaction with ammonium acetate in acetic acid gave the 1,2,4-triazines **38** in modest yield (Scheme 17) [27].



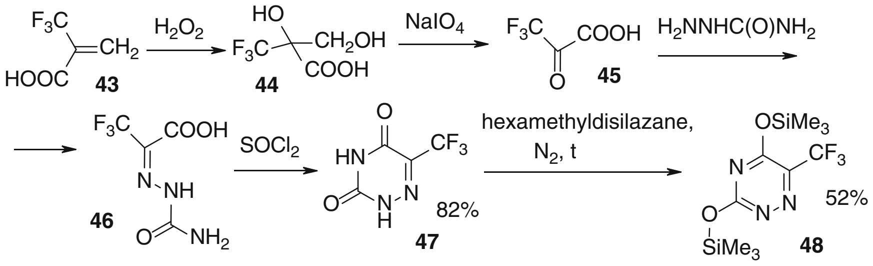
Scheme 17 Synthesis of 1,2,4-triazines **38**

The reaction of trifluoropyruvate **39** with 4-methylbenzoic acid amidrazone was carried out in refluxing ethanol to give 3-(p-tolyl)-6-trifluoromethyl-1,2,4-triazin-5(2H)-one **40** in 57 % yield. A 6-trfluoromethyl-1,2,4-triazine derivative **42** was synthesized in almost quantitative yield from **40** by chlorination followed by catalytic hydrogenation to remove chlorine substituent (Scheme 18) [28].



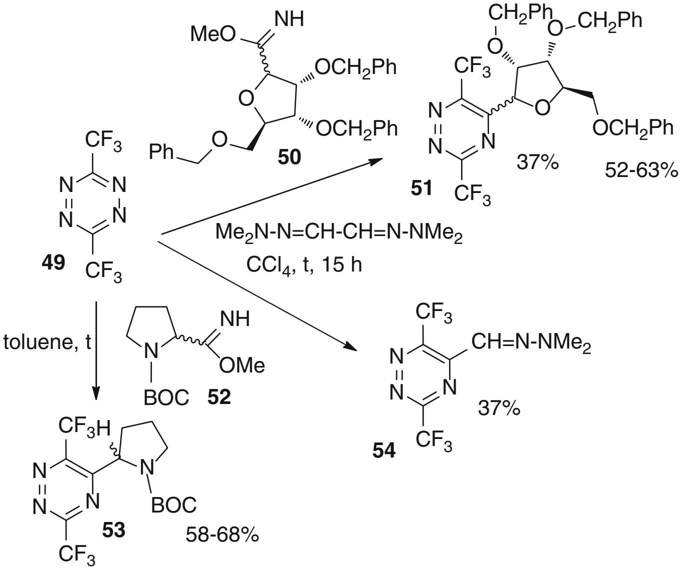
Scheme 18 Synthesis of triazine **42**

Bis(trimethylsilyl) ether of 5-trifluoromethyl-6-azauracil **48** was obtained for the synthesis of the corresponding β-D-deoxyribonucleoside and nucleotide. α-Trifluoromethacrylic acid **43** has been converted with hydrogen peroxide to α,β-dihydroxy-α-trifluoromethylpropionic acid **44**, which gave the hydrate of perfluoropyruvic acid **45** on treatment with sodium periodate. The semicarbazone **46** was cyclized using thionyl chloride to 5-trifluoromethyl-6-azauracil **47**, compound **47** was heated under reflux in hexamethyldisilazane under nitrogen atmosphere thus resulting in the formation of 6-trifluoromethyl-1,2,4-triazine **48** (Scheme 19) [29].



Scheme 19 Synthesis of 6-trifluoromethyl-1,2,4-triazine **48**

Examples of synthesis of trifluoromethyl-substituted 1,2,4-triazines by transformation of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **49** ring are presented at Scheme 20. The anomeric *C*-glycosyl precursors **50**, functionalized by an imidate group and appropriate for *C*-nucleoside synthesis were utilized as heterodienophiles in a *Diels-Alder* reaction with inverse electron demand to yield the *O*-benzyl protected 5-(β-D-ribofuranozyl)- and 5-(α-D-ribofuranosyl)-1,2,4-triazines **51** (Scheme 20) [30].



Scheme 20 Transformation of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **49** ring

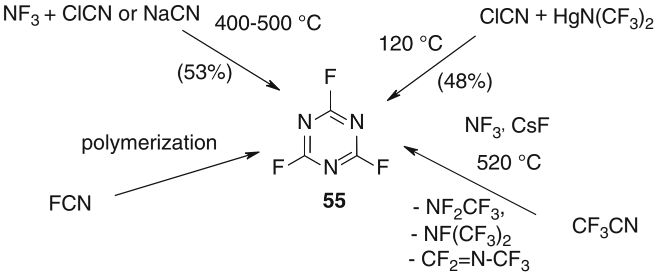
Analogues synthesis of 3,6-bis(trifluoromethyl)-1,2,4-triasines bearing (2′,3′-dideoxy-β-D-ribofuranosyl)- or (2′-deoxy-β-D-ribofuranosyl)-residue at position 5 was reported [31, 32]. A new strategy for a straightforward synthesis of chiral 5-(2′-pyrrolidinyl)-1,2,4-triazines **53** starting from (*S*)- and (*R*)-proline iminoester **52** utilizing as the key steps the inverse electron demand Diels–Alder reaction of tetrazine **49** was achieved (Scheme 20) [33]. Electron-rich C=N bond of the hydrazone $Me_2N\text{-}N=CH\text{-}CH=N\text{-}NH_2$ proved to be effective dienophiles towards the electron-deficient tetrazine **49**. The substituted 1,2,4-triazine **54** was formed by way of [4+2]cycloaddition and elimination of nitrogen [34].

3.3 Synthesis of Fluorine-Containing 1,3,5-Triazines

The most studied and widespread type of fluorinated triazines are 1,3,5-triazines. As well as their isomer compounds, fluorinated 1,3,5-triazines can be synthesized by several ways: (i) the formation of heterocyclic ring by means of cyclization reactions from fluorine-containing precursors; (ii) direct fluorination of triazines; (iii) nucleophilic displacement reactions of chlorinated triazines with the fluorine ion, and other synthetic procedures.

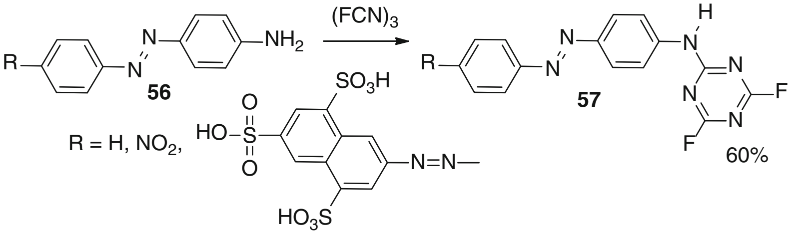
3.3.1 Cyclocondensation Reactions

Heating of a mixture of NaCN and NF_3 (or ClCN and NF_3) at 400–500 °C affords 2,4,6-trifluoro-1,2,3-triazine (cyanuric fluoride) **55** in a high yield (Scheme 21) [35]. The formation of triazine **55** is also observed on heating of chlorocyane with copper chloride at 300 °C [or on heating of chlorocyane with $HgN(CF_3)_2$ at 120 °C] [36], or by the reaction of trifluoroacetonitrile with cesium fluoride and NF_3 (Scheme 21) [37]. At room temperature, liquid cyanogen fluoride FCN is converted rapidly to polymeric materials, including cyanuric fluoride and a high-melting, water-sensitive solid polymer, but in the gas phase at atmospheric pressure it has been recovered partially after several weeks or under the conditions of polymerization [38].



Scheme 21 Synthesis of 2,4,6-trifluoro-1,2,3-triazine (cyanuric fluoride) **55**

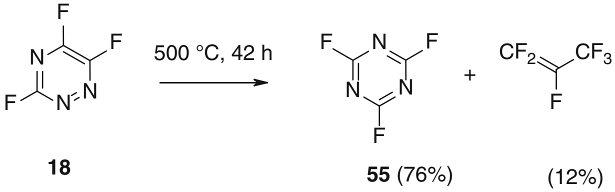
N-(4,6-Difluoro-1,3,5-triazin-2-yl)-N-ethyloctane-1-sulphonamide has been obtained from N-ethyloctane-1-sulphonamide and cyanuric fluoride [9]. The formation of 2,4-difluoro-1,3,5-triazine fragment has been exploited in the synthesis of dyes. The synthesis of triazine dyes has also been reported in a number of publications [39, 40] (Scheme 22). 2,4-Difluoro-6-arylamino-1,3,5-triazines **57** were obtained by the reaction of arylazoanilines **56** with cyanuric fluoride.



Scheme 22 Synthesis of 2,4-Difluoro-6-arylamino-1,3,5-triazines **57**

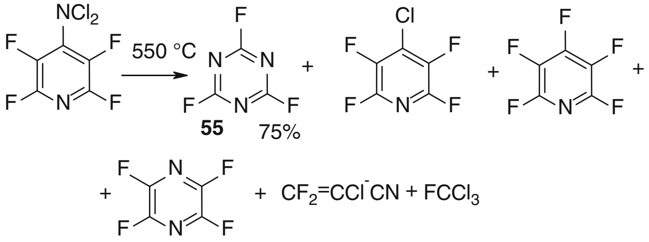
3.3.2 Ring Transformations

Heating of 3,5,6-trifluoro-1,2,4-triazine **18** at a high temperature (approximately 500 °C) for many hours gave 2,4,6-trifluoro-1,3,5-triazine **55**, as the ring transformation product, and perfluoropropylene (Scheme 23) [12].



Scheme 23 Transformation of 3,5,6-trifluoro-1,2,4-triazine **18** under heating

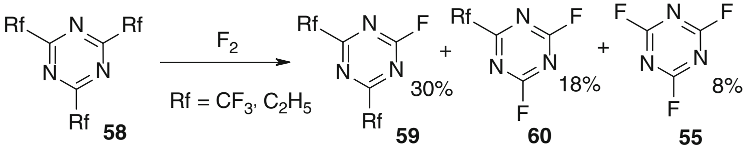
A rather complicated mixture of fluorinated compounds, including triazine **55**, is formed on heating of 4-dichloroamino-2,3,5,6-tetrafluoropyridine at 550 °C [41]. Such transformations are supposed to occur due to decomposition of one fluorinated heterocycle into fluorocyane followed by the construction of a new fluorinated triazine system (Scheme 24).



Scheme 24 Transformation of 4-dichloroamino-2,3,5,6-tetrafluoropyridine

3.3.3 Direct Fluorination

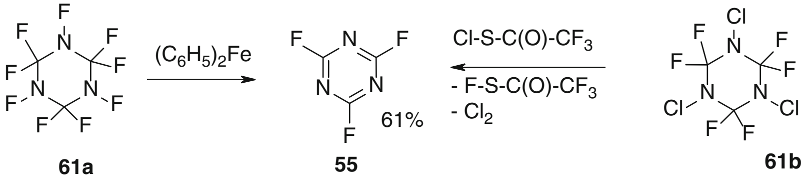
Fluorination of the ring has been shown to take place on treatment of perfluoroalkyl-1,3,5-triazines **58** with fluorine, thus resulting in the formation of a mixture of cyanuric fluoride **55** in addition to mono- and difluoro-1,3,5-triazines **59** and **60** (Scheme 25) [42].



Scheme 25 Fluorination of perfluoroalkyl-1,3,5-triazines **58**

3.3.4 Dehalogenation of Cyclic Halogenoamidines

Fluoroanhydride of cyanuric acid **55** was formed in a high yield by the defluorination reaction of perfluoro-1,3,5-triazacyclohexane **61a** by action of ferrocene (Scheme 26) [43]. Dehalogenation of $(NClCF_2)_3$ **61b** under the action of ClSC(O)CF$_3$ was reported (Scheme 26) [44].



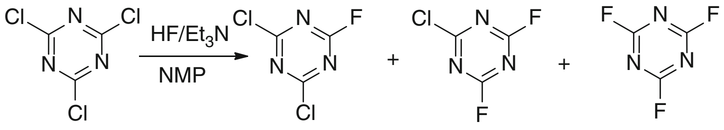
Scheme 26 Dehalogenation of cyclic halogenoamidines

Table 4 Fluorination of cyanuric chloride

Reaction conditions	Yield, %			Literature
	63	**64**	**55**	
SbF_3, $SbCl_3$, Cl_2, 160–180 °C	–	–	91	[47]
SF_4, 150–250 °C, autoclave, 12 h	–	–	40	[48]
SF_4, 150–250 °C, autoclave, 6 h	29	39	–	[48]
HF, 1-methyl-pyrrolidinone, $N(C_2H_5)_3$, 20–25 °C	–	–	90	[51]
CsF, 1-*n*-butyl-3-methylimidazolium hexafluorophosphate, 80 °C	11	3	10	[51, 53]
KSO_2F, 120–150 °C	3	11	31	[46]
KF, $C_3Cl_3N_3$/KF, 300 °C	–	–	48	[52]
AgF, 100 °C, 1 h	–	–	78	[53]
F_2, 125 °C	–			[50]

3.3.5 Replacement of Chlorine Atoms with Fluoride Ion

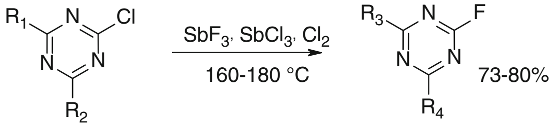
Replacement of chlorine atoms with fluoride ion is one of the main synthetic procedure to obtain fluorinated 1,3,5-triazines. Being depending on the reaction conditions and the nature of reagents, the reactions of cyanuric chloride with various fluorinating reagents lead to mono-, di- and trifluoro-1,3,5-triazines (Scheme 27, Table 4) [45–56]. A mixture of SbF_3, $SbCl_3$ and Cl_2 is an appropriate agent for total fluorination of cyanuric chloride **62.** Formation of trifluoroderivative **55** proceeds selectively in high yield under reaction of **62** with HF and $N(C_2H_5)_3$ in 1-methyl-pyrrolidinone at room temperature.



62 **63** **64** **55**

Scheme 27 Fluorination of cyanuric chloride **62**

It is worth to note that chlorine atoms both in the ring and in CCl_3 groups of compound **65** are subjected to the replacement reaction (Scheme 28) [47].

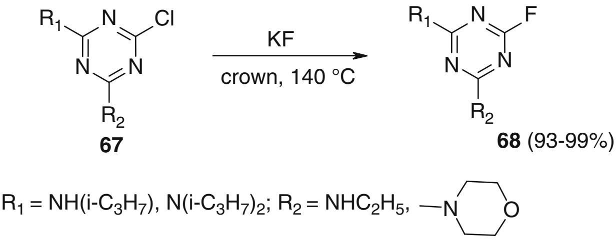


65 **66**

R^1	R^2	R^3	R^4	Yield, %
CCl_3	Cl	CF_3	F	73
CCl_3	CCl_3	CF_3	CF_3	79
C_6H_5	Cl	C_6H_5	F	73
C_6H_5	C_6H_5	C_6H_5	C_6H_5	80

Scheme 28 Synthesis of fluorinated 1,3,5-triazines **66**

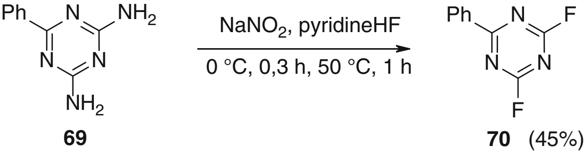
Fluorination of 2,3-diamino-6-chloro-1,3,5-triazines **67** with anhydrous KF has been shown to proceed smoothly in the presence of catalytical amounts of dicyclohexano-18-crown-6 (Scheme 29). Fluoro-1,2,4-triazines **68** were obtained in 93–99 % yields [7]. 2-Isopropylamino-4-ethylamino-6-fluoro-1,2,4-triazine **68** ($R^1 = NH(i\text{-}C_3H_7)$, $R^2 = C_2H_5$) was isolated in 66 % yield under similar reaction conditions with triethylpentadecylammonium bromide as the phase transfer catalyst [7].



Scheme 29 Synthesis of fluorinated 1,3,5-triazines **68**

3.3.6 The Baltz-Schiemann Reaction

2,4-Difluoro-1,3,5-triazine **70** was obtained by diazotization of the corresponding diamino compound **69** followed by thermolysis of the resulting diazonium tetrafluoroborate (Scheme 30) [57].

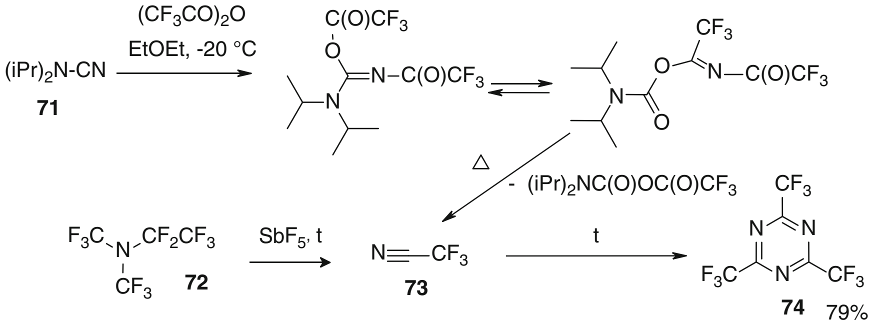


Scheme 30 Synthesis of fluorinated 1,3,5-triazines **70**

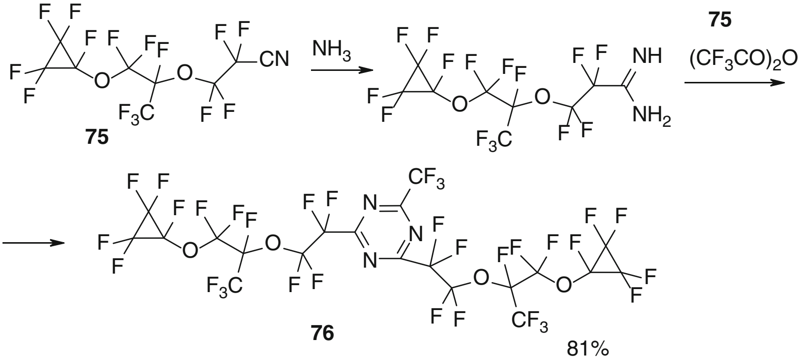
The main synthetic approaches to trifluoromethyl substituted 1,3,5-triazines are trimerization of CF_3CN [58], cyclocondensation process based on imidoylamidines [59], cyanoguanidines [60] or biguanides [61] and also fluorination of trichloromethyl-1,3,5-triazines [47, 62].

For example, trifluoroacetonitrile **73** trimerizes to give 2,4,6-tris(trifluoromethyl)-1,3,5-triazine **74** [63]. Monomeric CF_3CN was generated by reaction of diisopropylcyanamide **71** and trifluoroacetic anhydride [58] or from perfluoroethyldimethylamine **72** [6] (Scheme 31).

Di(pentafluorocyclopropanyl)-substituted triazine **76** was prepared from nitrile **75** by reaction with ammonia followed by acylation-cyclization with trifluoroacetic anhydride (Scheme 32) [64].

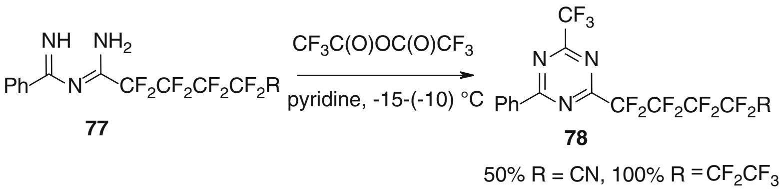


Scheme 31 Synthesis of 2,4,6-tris(trifluoromethyl)-1,3,5-triazine **74**



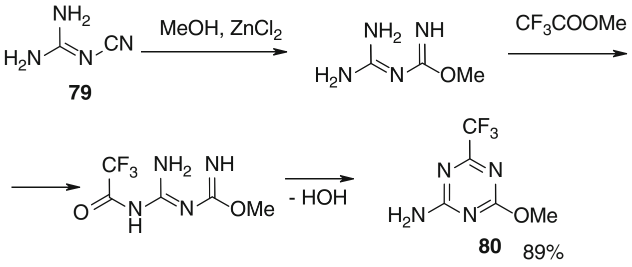
Scheme 32 Synthesis of fluorinated 1,3,5-triazine **76**

By the method of acylation-cyclodehydration of imidoylamidines **77** 1,3,5-triazines **78** have been prepared (Scheme 33) [59]. Synthesis of 2-trifluoromethyl-4,6-bis(2,3-dichloro-1,1,2,3,3-pentafluoro)-1,3,5-triazine from 3,4-dichloro-2,2,3,4,4-pentafluorobutyronitril, NH_3 and trifluoroacetic anhydride was reported [65].



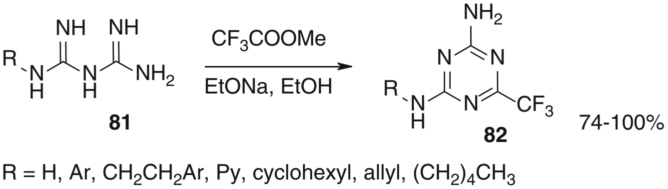
Scheme 33 Synthesis of fluorinated 1,3,5-triazine **78**

2-Amino-4-trifluoromethyl-6-methoxy-1,3,5-triazine **80** can be easily prepared starting from cyanoguanidine **79** by a zinc chloride-catalysed process (Scheme 34) [60].



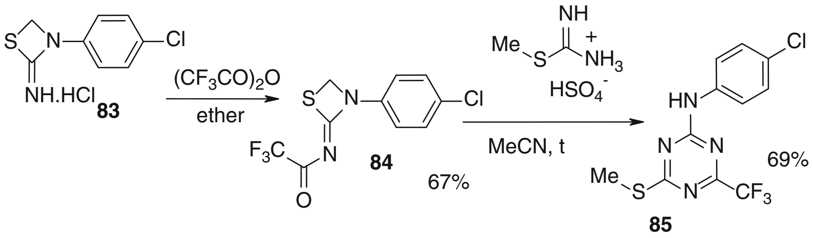
Scheme 34 Synthesis of fluorinated 1,3,5-triazine **80**

Cyclocondensation of substituted biguanides **81** with methyl trifluoroacetate in the presence of catalytic amounts of sodium ethylate gave 2-amino-4-(substituted amino)-6-trifluoromethyl *sym*-triazines **82** (Scheme 35) [66–72]. A rapid and efficient synthesis under microwave irradiation has been developed for various substituted 1,3,5-triazines that can serve as versatile building blocks for both supramolecular and medicinal chemistry [61, 73].



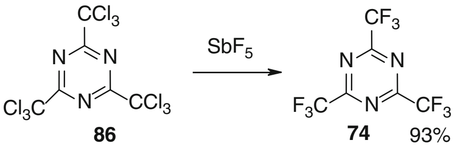
Scheme 35 Synthesis of fluorinated 1,3,5-triazines **82**

2-Imino-1,3-thiazetidine **83** was used as precursor in the synthesis of triazine **85** (Scheme 36) [74]. Reaction of **83** with trifluoroacetic anhydride leads to 2-trifluoromethylimino-3-(4-chlorophenyl)-1,3-thiazetidine **84**, the treatment of **84** with S-methylisothiourea sulfate results in trifluoromethyl substituted triazine **85**.



Scheme 36 Synthesis of fluorinated 1,3,5-triazine **85**

2,4,6-Tris(trichloromethyl)-1,3,5-triazine **86** was transformed to trifluoromethylderivative **74** under the action of SbF_5 (Scheme 37) [62].



86 **74**

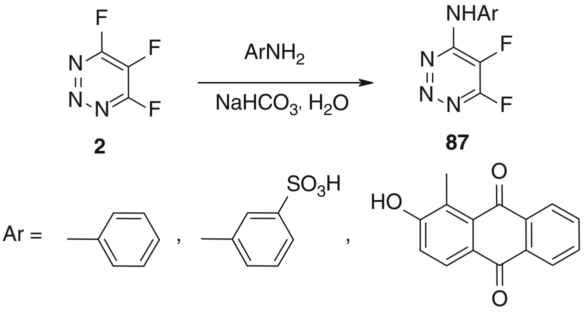
Scheme 37 Synthesis of 2,4,6-tris(trifluoromethy1)-1,3,5-triazine **74**

4 Chemical Properties

The main reactions of fluorine-containing triazines are connected with attack on the carbon atom bearing fluorine, which results to replacement of the fluorine atom or cycle transformation.

4.1 *Chemical Properties of 1,2,3-Triazines*

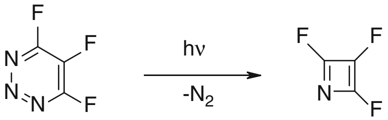
Aromatic amines are capable to displace fluorine atoms in trifluroro-1,2,3-triazine **2** to give 4-substituted products **87** (Scheme 38) [75–77].



2 **87**

Scheme 38 Amino-defluorination process in trifluroro-1,2,3-triazine **2**

Being UV-irradiated 4,5,6-trifluoro-1,2,3-triazine **2** is transformed into trifluoroazet **88** (Scheme 39) [78].

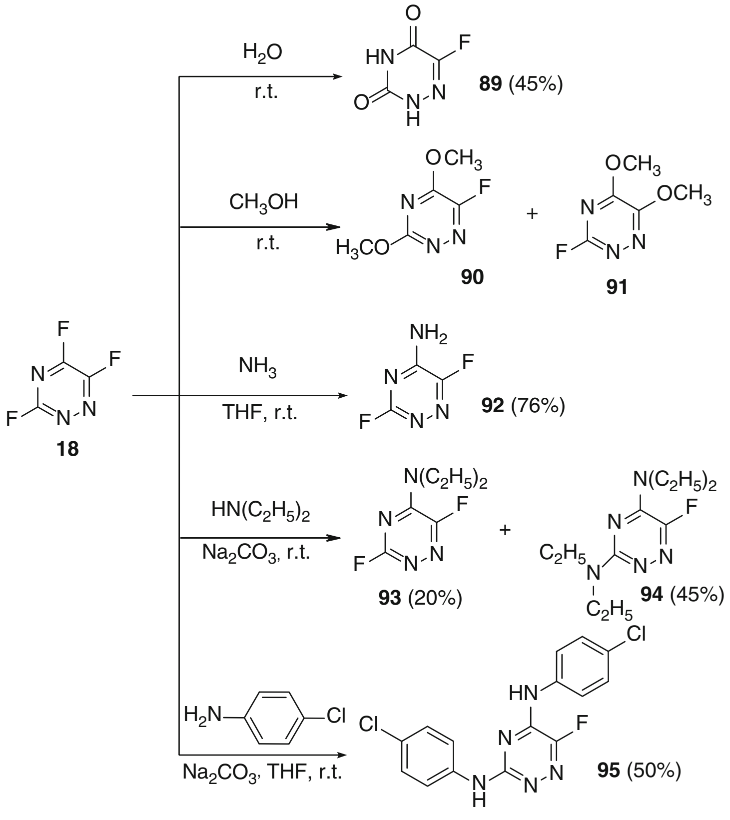


2 **88**

Scheme 39 Transformation of 4,5,6-trifluoro-1,2,3-triazine **2** under UV-irradiation

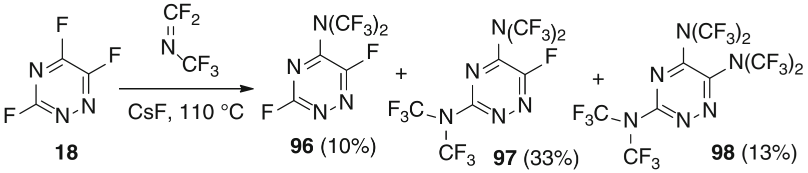
4.2 Chemical Properties of 1,2,4-Triazines

A number of transformations involving the displacement of fluorine atoms in fluorinated 1,2,4-triazines have been described. In case of 3,5,6-trifluoro-1,2,4-triazine **18** the leaving mobility of fluorine atoms in these displacement reactions is decreasing as follows $F^5 > F^3 > F^6$. In accordance with this sequence the hydrolysis of 1,2,4-triazine **18** results in the formation of 6-fluoro-1,2,4-triazine-3,5-(2H,4H)-dione **89** (Scheme 40) [20]. The reaction of compound **18** with methanol in a sealed tube afforded 3,5-dimethoxy-6-fluoro- and 5,6-dimethoxy-3-fluoro-1,2,4-triazines **90** and **91** in the ratio 1:2 in total yield of 46 % [20]. Reactivity of 3,5,6-trifluoro-1,2,4-triazine **18** towards N-nucleophiles can be illustrated by the reactions with ammonia (leading to 5-amino-3,6-difluoro-1,2,4-triazine **92**), diethylamine and 4-chloroaniline. The reaction of **18** with diethylamine affords two products, 5-diethylamino-3,6-difluoro-1,2,4-triazine **93** and 3,5-bis(diethylamino)-6-fluoro-1,2,4-triazine **94** (Scheme 40) [20], while the only compound **95** was obtained from the reaction of **18** with 4-chloroaniline.



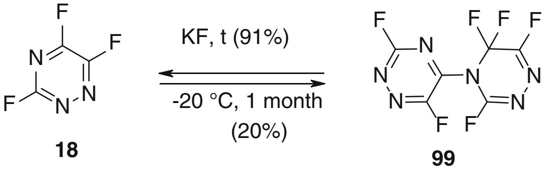
Scheme 40 Displacement of fluorine atoms in fluorinated 1,2,4-triazines

It is worth to note that the replacement of fluorine atoms in 3,5,6-trifluoro-1,2,4-triazine **18** by action of bis(trifluoromethyl)amino anion (the latter can be obtained from perfluoro-2-azapropene and cesium fluoride) provides a mixture of mono-, di- and trisubstituted perfluorodimethylamino-1,2,4-triazines **96–98** (Scheme 41) [12].



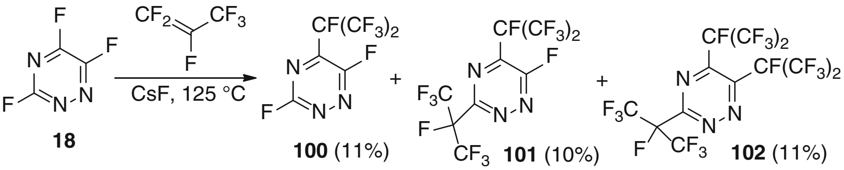
Scheme 41 Interaction of **18** with bis(trifluoromethyl)amino anion

When 3,5,6-trifluoro-1,2,4-triazine **18** was kept in vacuo at -20 °C for 1 month in a Pyrex ampoule the dimeriration product, 3,6-difluoro-5-(3,5,5,6-tetrafluoro-4,5-dihydro-1,2,4-triazine-4-yl)-1,2,4-triazine **99,** was shown to be formed (Scheme 42) [20]. The dimer **99** was passed over potassium fluoride at 250 °C to form triazine **18**.



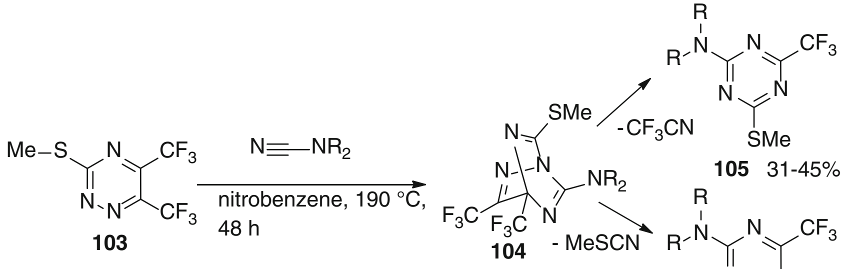
Scheme 42 Dimeriration of 3,5,6-trifluoro-1,2,4-triazine **18**

Incorporation of perfluoroisopropyl groups into trifluoro-1,2,4-triazine takes place smoothly in the reaction of **18** with hexafluoropropene and cesium fluoride without of any solvent [12]. When the reaction is carried out at 125 °C for 25 min a mixture of 5-perfluoroisopropyl-derivative **100** and 3,5-di- and 3,5,6-tri (perfluoroisopropyl)-1,2,4-triazines **101, 102** are formed (Scheme 43), while the formation of trisubstituted derivative **102** (yield 52 %) takes place on heating at 110 °C for 2 h.



Scheme 43 Reaction of **18** with hexafluoropropene

A number of ring transformations and reactions involving the displacement of substituents such as SMe-group in trifluoromethyl containing 1,2,4-triazines have been described. *N*-substituted cyanamides participate in cycloaddition exclusively across C-5/N-2 of the 1,2,4-triazine nucleus **103** yielding the bicycle **104** as nonisolable intermediate. Elimination of trifluoroacetonitrile leads to the 1,3,5-triazines **105** as the main reaction products. Besides, the 1,2,4-triazines **106** are formed by loss of methyl thiocyanate (Scheme 44) [28].

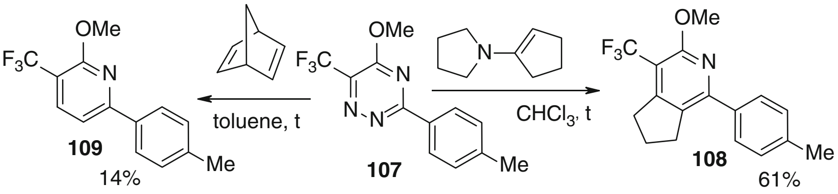


$NR_2 = NMe_2$ (a), pyrrolidin-1-yl (b), morpholin-4-yl (c), piperidin-1-yl (d)

Yield of **105a** 40%, **105b** 31%,**105c** 45%, **105d** 34%;
106a 36%, **106b** 21%,**106c** 22%, **106d** 21%

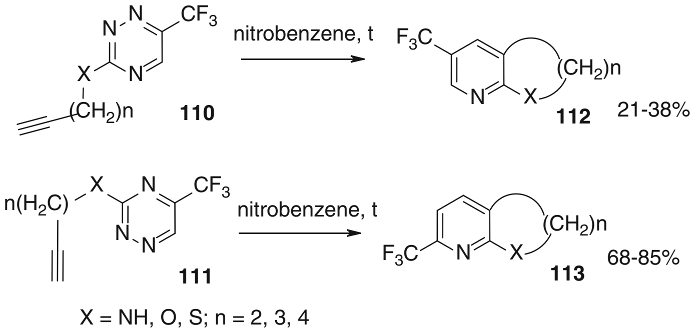
Scheme 44 Transformations and displacement of SMe-group in trifluoromethyl containing 1,2,4-triazines

When the 5-methoxy derivative **107** was reacted with enamine in refluxing chloroform, pyridine **108** was obtained (Scheme 45) [28]. Diels-Alder reaction of triazine 5 with norbornadiene leads to formation of pyridine **109** (Scheme 45). Low yield of **109** clearly shows that this Diels-Alder reaction proceeds in an inverse electron demand manner [28].



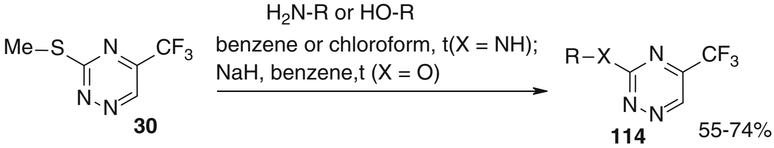
Scheme 45 Diels-Alder reactions of triazine **107**

Annulated pyridines **112** or **113** were formed on heating of triazines **110** or **111** bearing at position 3 NH-$(CH_2)_n$-C≡CH, O-$(CH_2)_n$-C≡CH or S-$(CH_2)_n$-C≡CH groups in chlorobenzene or diphenylether (Scheme 46) [23, 24]. This transformation is an example of intramolecular Diels-Alder reaction of 1,2,4 triazines accomplished with nitrogen elimination.



Scheme 46 Transformations of triazines **110** or **111**

Nucleophilic displacement of the thiomethyl group in triazines **30** is described (Scheme 47) [23, 24, 80]. This reaction is valuable approach to broad variety of trifluoromethylated triazines.



Scheme 47 Nucleophilic displacement of the thiomethyl group in triazines **30**

4.3 Chemical Properties of 1,3,5-Triazines

The chemistry of fluorinated 1,3,5-triazines is not as well studied as the chemistry of their chloro derivatives. In case of fluorotriazines the reactions directed on the ring nitrogen atoms, displacement of fluorine atoms and reactions on carbon atoms on the ring with retention of the fluorine atoms appear to be the most characteristic ones. In this section the N-alkylation and N-acylation reactions, as well as replacement of fluorine atoms by a variety of nucleophiles will be considered. Metallation of fluorotriazines and synthesis on the basis of organometallic compounds, as well as the cross-coupling reactions were described. Also several examples of photochemical reactions and transformations are presented.

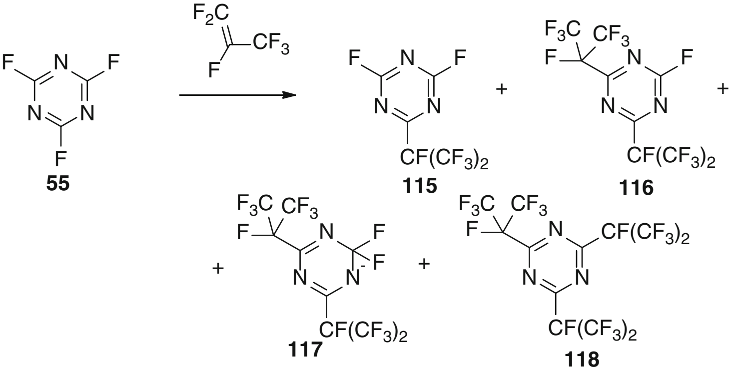
4.3.1 Replacement of Fluorine Atoms

Nucleophilic replacement of fluorine atoms in azaaromatic compounds can be performed under rather mild reaction conditions, and this method is certainly one of the most effective approaches to their functionalization. Incorporation of perfluoroisopropyl groups into 2,4,6-trifluoro-1,3,5-triazine **55** proceeds smoothly

Table 5 The reaction of cyanuric fluoride **55** with hexafluoropropene

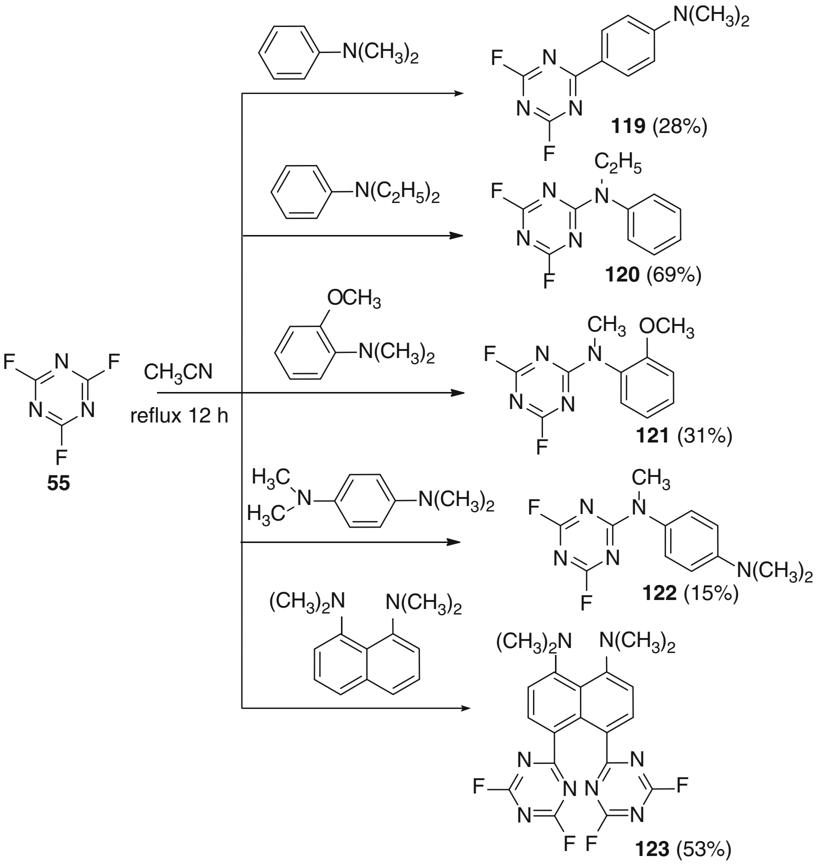
Reaction conditions	Yield, % **115**	**116**	**117**	**118**	Ref
CsF, 125 °C	11	10	–	11	[11]
CsF, 110 °C, 2 h				52	[11]
KF, 70 °C, 19 h, sulfolane	36	15	–	8	[83]
PSHF, 72 h, sulfolane	35	8	–	–	[47]
$N(C_2H_5)_3$, 60 °C, 48 h, CH_3CN	11	29	40	16	[82]
NCH_3, 60 °C, 48 h, CH_3CN	11	16	40	–	[82]
NCH_3, r.t., 10–12 h	20	37	–	36	[83]
NCH_3, 60 °C, no solvent, 48 h	–	–	–	95	[82]

by action of hexafluoropropene and cesium fluoride without of any solvent (Scheme 48, Table 5) [11, 81–83]. Trisubstituted derivatives **118** were formed in 52 % yield at 110 °C during 2 h. If reaction was carried out at 125 °C within 25 min the mixture of trisubstituted derivative **118** and 5-perfluoroisopropyl-1,2,4-triazine **115** and 3,5-di-(perfluoroisopropyl)-1,2,4-triazine **116** (Scheme 48) was isolated.



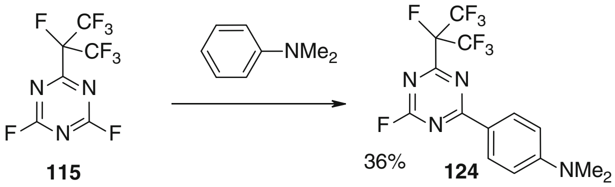
Scheme 48 Incorporation of perfluoroisopropyl groups into 1,3,5-triazine **55**

It is worth noting that 2,4,6-trifluoro-1,3,5-triazine **55** is less active than cyanuric chloride in the reaction of with aniline (Scheme 49) [84]. N,N-Dimethylaniline and 1,8-bis(dimethylamino)naphthalene react with cyanuric fluoride **55** as C-nucleophiles to give 2,4-difluoro-6-(4-dimethylaminophenyl)-1,3,5-triazine **119** and 1,8-bis(dimethylamino)-4,5-(2,4-difluoro-1,3,5-triazinyl-6)naphthalene **123** (Scheme 49) [8]. Contrary to it, N,N-diethylaniline, and *ortho*- or *para*-substituted N,N-dimethylanilines react with trifluoro-1,3,5-triazine **55** as N-nucleophiles. These reactions are accompanied by elimination of N-alkyl group and the formation of 2,4-difluoro-6-arylamino-1,3,5-triazines **120–122** (Scheme 49).



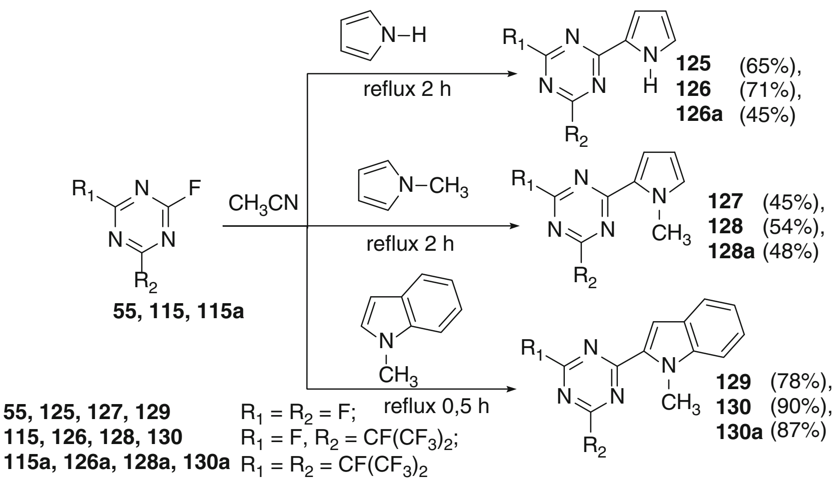
Scheme 49 Reactions of cyanuric fluoride **55**

In a similar way, on treatment of perfluoro-1,3,5-triazine **115** with dimethylaniline 2-fluoro-4-heptafluoroisopropyl-6-(4-dimethylaminophenyl)-1,3,5-triazine **124** was obtained in 36 % yield (Scheme 50) [8].



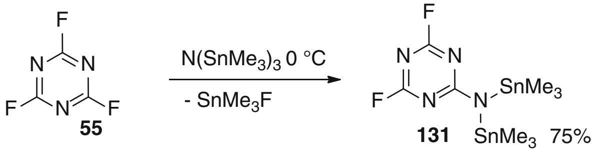
Scheme 50 Formation of triazine **124**

Replacement of fluorine atoms in triazines **55, 115** and **115a** take place also by action of pyrrole, N-methylpyrrole and N-methylindole resulting in the formation of the corresponding 1,3,5-triazines **125–130** (Scheme 51) [8].



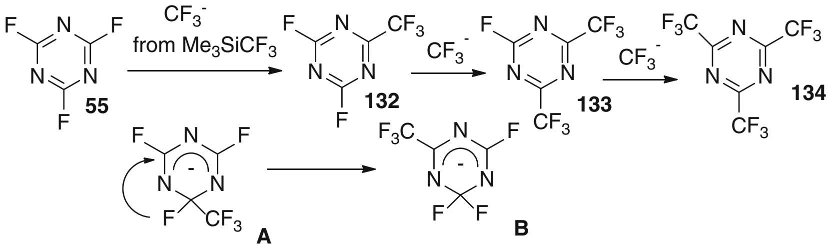
Scheme 51 Replacement of fluorine atoms in triazines **55, 115** and **115a**

In a similar manner, the reaction of cyanuric fluoride **55** with tris(trimethylstannyl) amine in dry ether at 0 °C leads to the formation of 2,4-difluoro-6-[di(trimethylstannyl)]-amino-1,3,5-triazine **131** (Scheme 52) [5].



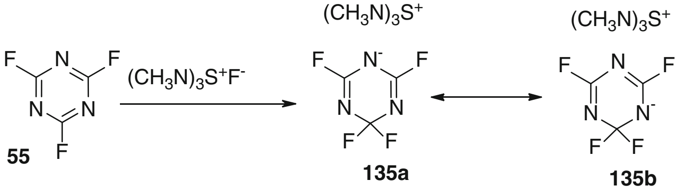
Scheme 52 Reaction of cyanuric fluoride **55** with tris(trimethylstannyl)amine

Reaction pathway for substitution of fluorine atom in 2,4,6-trifluoro-1,3,5-triazine **55** under the action of trifluoromethyl anion has been studied [4] (Scheme 53). Since **$C_3N_3F_4^-$** can act as a potential fluoride donor, initial reaction takes place between **$C_3N_3F_4^-$ (A)** and Me_3SiCF_3 forming a reactive silane, a source of the elusive CF_3 anion, which can then attack the neutral triazine (Scheme 53). Through **A** → **B** rearrangement, elimination, and further addition reactions the observed. As a result products **132**, **133** and **134** are formed (Scheme 53).



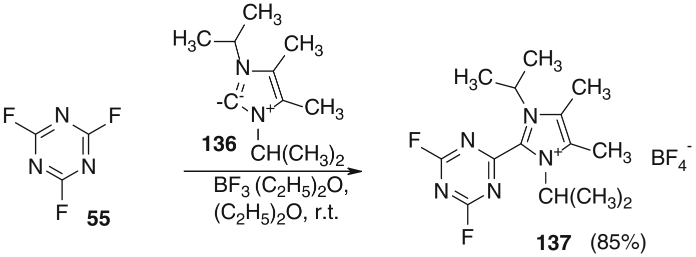
Scheme 53 Substitution of fluorine atoms in 2,4,6-trifluoro-1,3,5-triazine **55**

The anion $C_3N_3F_4$ (**135**) was prepared using TASF as the fluoride source via a simple fluoride addition to a carbon centre of $C_3N_3F_3$. After removal of the solvent and all volatile products in vacuo, a colourless solid was isolated in quantitative yield (Scheme 54). The compound shows two signals in the ^{19}F NMR spectrum, due the presence of two magnetically nonequivalent fluorine groups. This indicates the absence of fast intramolecular fluorine exchange, which was found e.g. in cyclic fluorophosphazenates [4, 85].



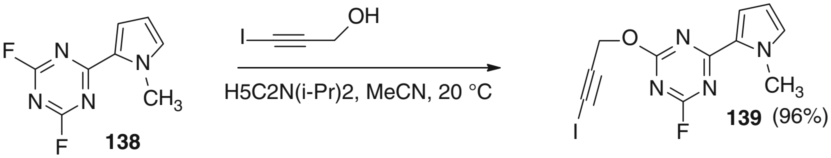
Scheme 54 Fluoride addition to a carbon centre of $C_3N_3F_3$

2,4,6-Trifluoro-1,3,5-triazine **55** reacts with 2,3-dihydro-1,3-isopropyl-4,5-dimethylimidazol-2-ylidene tetrafluoroborate **136** resulting in replacement of one fluorine atom to yield difluoro-1,3,5-triazine **137** (Scheme 55) [8].



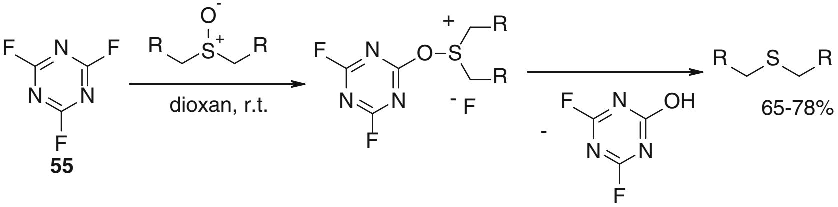
Scheme 55 Interaction of **55** with 2,3-dihydro-1,3-isopropyl-4,5-dimethylimidazol-2-ylidene tetrafluoroborate **136**

The reaction of 2,4-difluoro-6-(1-methylpyrrolyl-2)-1,3,5-triazine **138** with iodpropargyl alcohol affords the product **139** due to replacement of one fluorine atom (Scheme 56) [86].



Scheme 56 Formation of fluorotriazine **139**

Deoxygenative ability of cyanuric fluoride **55** for sulfoxides has been shown (Scheme 57) [87]. In contrast to cyanuric chloride no concomitant formation of undesired halogenated sulfides forms due to relatively low nucleophilicity of the fluoride ion.

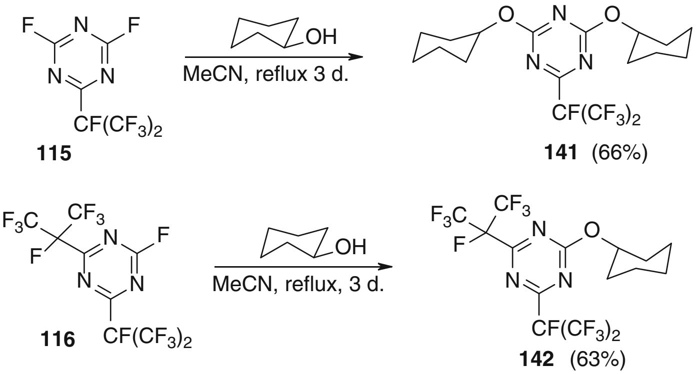


Scheme 57 Deoxygenative ability of cyanuric fluoride **55**

Replacement of fluorine atoms in 2,4-difluoro-6-heptafluoro-*iso*-propyl- and 2-fluoro-4,6-bis(heptafluoro-*iso*-propyl)-1,3,5-triazines **115** and **116** takes place quantitatively on reflux of **115** or **116** with methanol, isopropanol or phenols in acetonitrile (Scheme 58) [83].

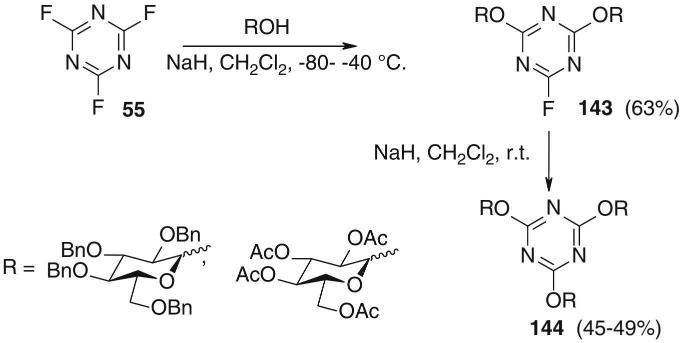
Scheme 58 Replacement of fluorine atoms in compounds **115** and **116**

Heating of compound **115** with cyclohexanol has been established to afford 2,4-dicyclohexyloxy-6-heptafluoro-*iso*-propyl-1,3,5-triazine **141**, while 2-cyclohexyloxy-4,6-bis(heptafluoro-*iso*-propyl)-1,3,5-triazine **142** was formed from compound **116** (Scheme 59) [83].



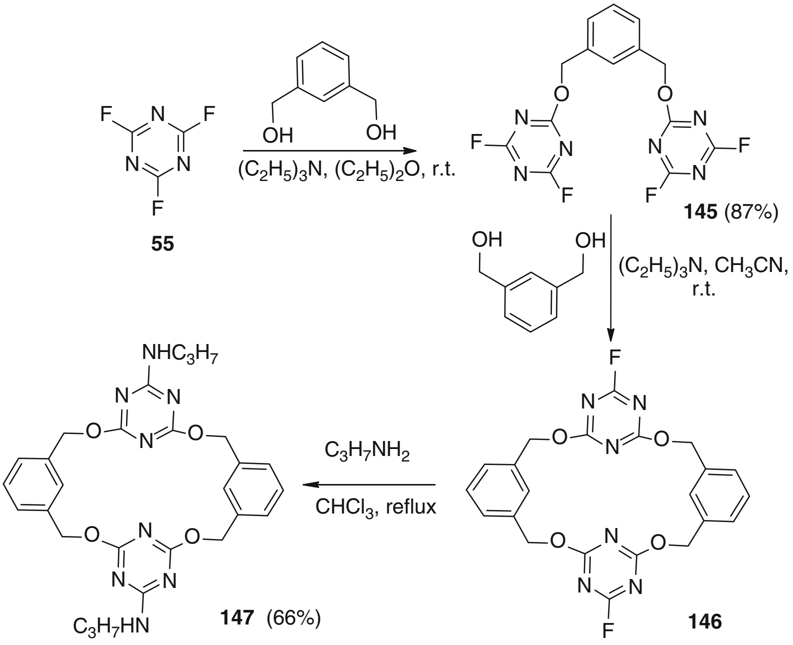
Scheme 59 Synthesis of cyclohexyloxy-derivatives of fluorinated triazines

It is known [88] that replacement of fluorine atoms in cyanuric fluoride **55** with tetra-O-benzyl- or tetra-O-acetylglucose takes place consequently with the formation of di- and trisubstituted 1,3,5-triazines **143** and **144** (Scheme 60).



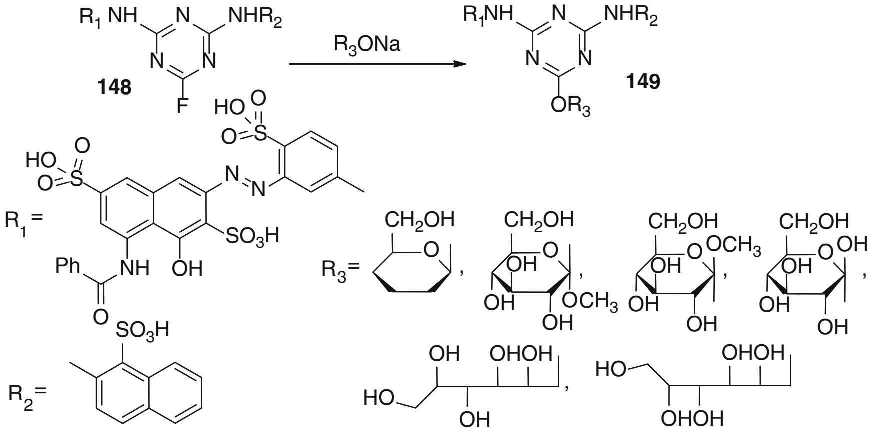
Scheme 60 Replacement of fluorine atoms in **55** with tetra-O-benzyl- or tetra-O-acetylglucose

The ability of fluorine atoms in cyanuric fluoride **55** to be replaced by action of O-nucleophiles can be exploited for the synthesis of calix[2]arene-[2]triazines **146** and **147** [89]. The reaction of **55** with 1,3-phenylenedimethanol leads to the formation of fluoro compound **145**, and then to calix **146**. Remaining fluorine atoms in the triazine fragments of calix **146** can be replaced easily by action of amines (Scheme 61).



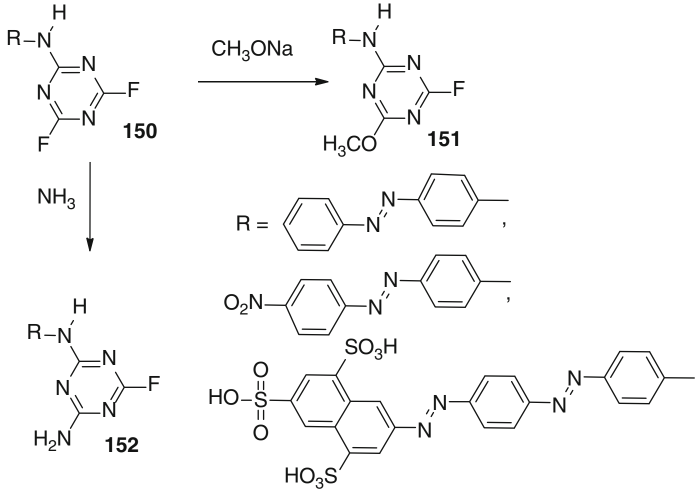
Scheme 61 Synthesis of calix[2]arene-[2]triazines **146** and **147**

Reaction of 2,4,6-trifluoro-1,3,5-triazine **55** with 1-amino-8-naphthol-3,6-disulfonic acid provides 1-(4′,6′-difluoro-1′,3′,5′-triazyn-2′-yl)amino-8-naphthol-3,6-disulfonic acid in 95 % yield [90]. Substitution of fluorine atoms in fluorotriazine dye **148** with the alkoxides, generated from tetrahydropyran-2-methanol, α- and β-methylglucopyranoside, D-sorbitol, D-mannitol and D-glucose, has been found to lead to the corresponding conjugates **149** (Scheme 62) [91].



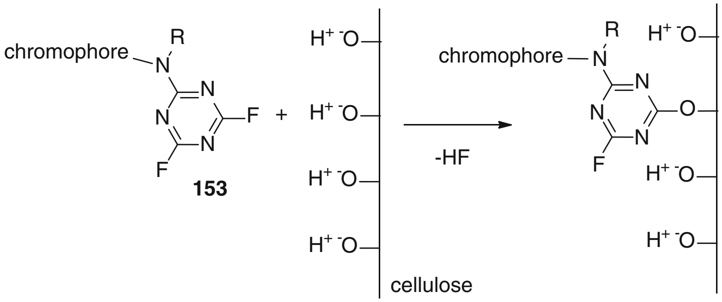
Scheme 62 Synthesis of derivatives **149**

Replacement of one of fluorine atoms in 2,4-difluoro-6-(4-arylazophenyl)-amino-1,2,4-triazines **150** with methoxy or amino group is used for the synthesis of fluorotriazine dyes **151** and **152**, which are effective for cotton coloring (Scheme 63) [39, 40].



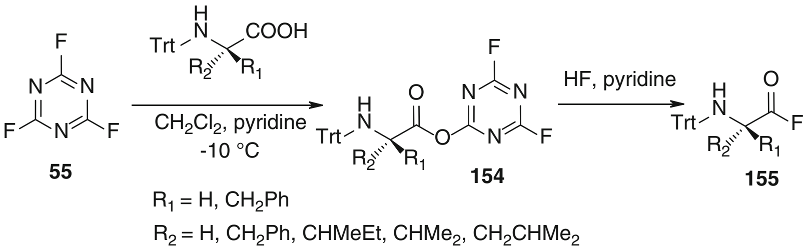
Scheme 63 Synthesis of fluorotriazine dyes **151** and **152**

The chemical process of replacement of fluorine atoms has found its practical application for fixing of yellow and dark blue fluorotriazine dyes **153** on cellulose (Scheme 64) [92–94].



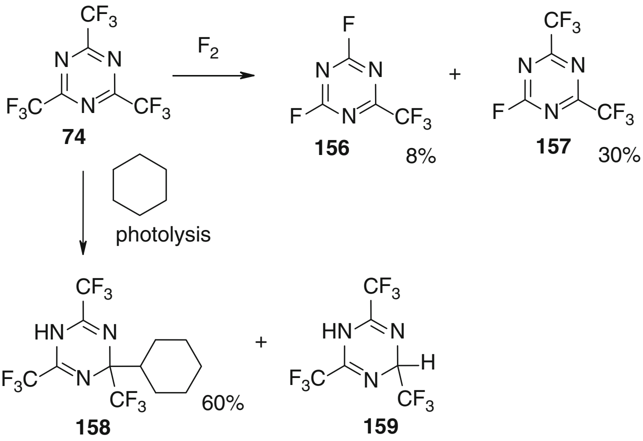
Scheme 64 Fixing of yellow and dark blue fluorotriazine dyes **153** on cellulose

Replacement of three fluorine atoms in cyanuric fluoride **55** was applied for construction biologically active molecules of deazapurine type [95]. Cyanuric fluoride mediated reaction of chiral Nα-tritylamino acids leads to the corresponding acyl fluorides **155** which are powerful acylating agents for peptide synthesis (Scheme 65) [96].



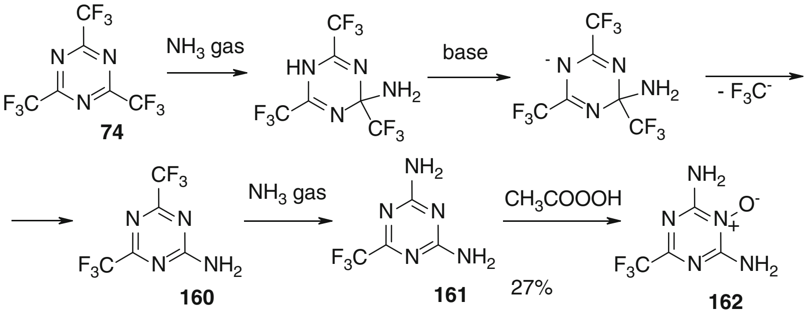
Scheme 65 Acyl fluorides **155**, powerful acylating agents for peptide synthesis

Reactions of replacement of SMe [79], trichloromethyl [97] or trifluoromethyl groups represent effective approaches for modifications of trifluoromethyl containing 1,3,5-triazines. Direct vapor-phase fluorination of tris-(trifluoromethy1)-s-triazine **74** has been studied and was found that the perfluoroalkyl groups of **74** were progressively replaced by fluorine to give mixture of 2,4-difluoro-6-trifluoromethyl-s-triazine **156** and 2,4-bis-(trifluoromethyl)-6-fluoro-s-triazine **157** (Scheme 66) [98]. Photoirradiation of tris-(trifluoromethy1)-*s*-triazine in cyclohexane leads to a mixture of adduct **158** and dihydrocompound **159** (Scheme 66) [99].



Scheme 66 Transformations of tris-(trifluoromethy1)-*s*-triazine

Diamine compound **161** was obtained in the reaction of tris(trifluoromethyl)-s-triazine **74** with ammonia. The reaction was presumed to proceed through addition-elimination mechanism as shown at Scheme 67 from the fact that 1,4-adduct was obtained, when ammonia gas was bubbled into the ether solution of the s-triazine [100].

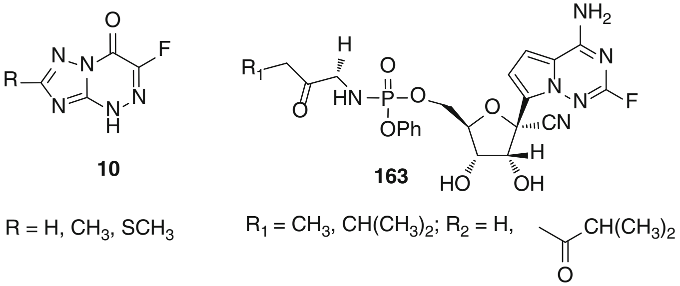


Scheme 67 Reaction of tris(trifluoromethyl)-s-triazine **74** with ammonia

Transformation of diamino-derivative **161** to N-oxide **162** was reported via oxidation with peracetic acid [101]. 2,4,6-Tris-(trifluoromethyl)-1,3,5-triazine **74** reacts with ethanol an the presence of hydrochloric acid to form ethyl trifluoroacetate [62].

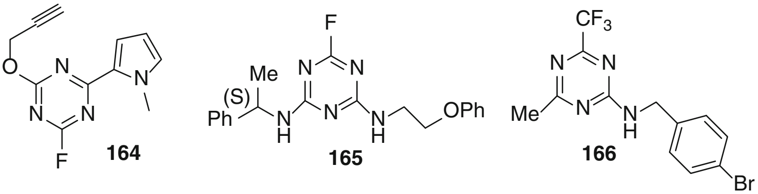
5 Application of Fluorinated Triazines

2-R-6-Fluoro-1,2,4-triazolo[5,1-*c*][1,2,4]triazin-7(4*H*)-ones **10** were shown to be active against flu A virus [16], while 1′-substituted carbonucleosides **163** bearing the fragment of pyrrolo[5,1-*f*][1,2,4]triazine were reported to possess antiviral activity (Scheme 68) [102].



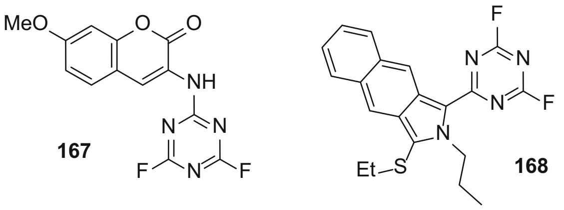
Scheme 68 Annelated fluorotriazines possessing antiviral activity

2,4,6-Trifluoro-1,3,5-triazines are widely used as starting materials for the synthesis of dyes, sensors, and biologically active compounds. A series of synthetic dyes containing one or two fluorine atoms, for example **148** [91], **151, 152** [39, 45], **54** [86, 92, 94] have been described. Also patents [103–112] are dedicated to fluorotriazine dyes. The reaction of cyanuric fluoride with amines has been used for the synthesis of analogs of the anticancer drug trimelamol which is 2,4,6-tris-[(hydroxymethyl)methylamino]-1,3,5-triazine. That is why cytotoxic properties of its analogs, such as 2-fluoro-4,6-bis[(2,2,2-trifluoroethyl)amino]-1,3,5-triazine and 2-fluoro-4,6-*bis*(propargylamino)-1,3,5-triazine, towards a variety of tumor cell lines in vitro have been studied. They revealed that 2,4,6-trisubstituted derivatives proved to be more active than 2-fluoro-4,6-disubstituted analogs [113]. Compound **164** was shown to inhibit enzyme Akt1-kinase [114], while aminotriazine **165** was found to act as 5-HT$_7$ receptor antagonist (binding affinity $K_i = 10$ nM) [115]. 6-(4-Bromobenzylamino)-2-methyl-4-trifluoromethyl-1,3,5-triazine **166** was found to possess strong pre- and post-emergence herbicidal activities (Scheme 69) [97].



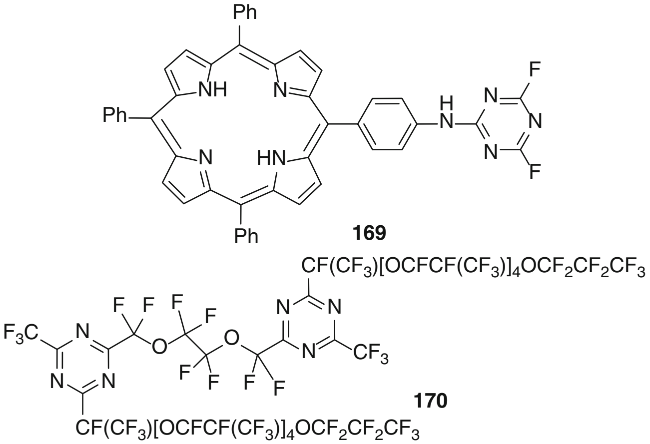
Scheme 69 Structure of fluorotriazines **164–166**

3-(4,6-Difluorotriazinyl)amino-7-methoxycoumarin (FAMC, **167**) is useful for determination of antiviral drug amantadine by high-performance liquid chromatography. Amantadine was derivatized quantitatively into fluorescent compound through the amino group treatment with FAMC, this method gave satisfactory results with respect to recovery and precision to quantify amantadine spiked in urine [116]. 3-(Difluoro-1,3,5-triazinyl)-1-(ethylthio)-2-n-propylbenz[f]isoindole (**168**), which reacts with phenolic hydroxyl groups, can use as a fluorescence derivatization reagent for estrogens in high-performance liquid chromatography (Scheme 70) [117].



Scheme 70 Structure of fluorotriazines **167**, **168**

Receptor for naphthalene diimide guest with efficient quenching of prophyrin fluorescence was obtained by replacement of two fluorine atoms in compound **169** by n-pentylamine [118]. Perfluoroalkyl-s-triazines **170** can be used as high-temperature fluids (Scheme 71) [119].



Scheme 71 Structure of fluorotriazines **169**, **170**

6 Conclusion

It is worth to mention that triazines and their fluorinated derivatives continue to be important for applications in medicine as well as intermediates for dyes and sensors.

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