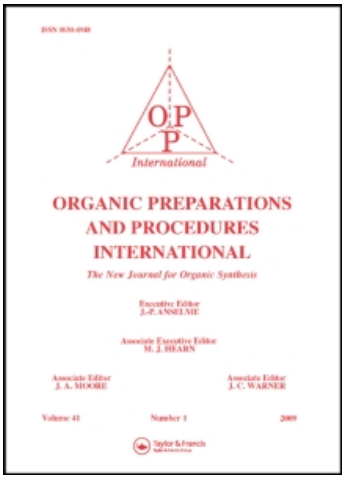

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TRIFLUOROMETHYL AND PERFLUOROALKYL DERIVATIVES OF AZOLES. A REVIEW

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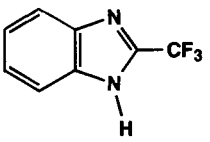
INTRODUCTION

The chemistry of azoles bearing substituents such as CF_3 and its higher homologues (represented, as a whole, by R_F) is experiencing a rapid development, due to the biological properties of the resulting compounds, but also due to interest in understanding the modification of the physico-chemical properties brought about by these peculiar substituents. It has been pointed out that the introduction of a trifluoromethyl group into a heterocycle frequently results in a much more potent activity than that of the parent compound, a fact which is probably related to the very high lipophilicity of perfluoroalkyl substituents.

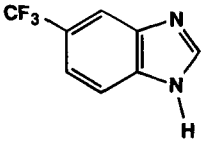
There are few books or reviews dealing with these compounds. Schieman and Cornils,[1] describe only four such compounds which will be reported under this reference in the appropriate sections. McClinton and McClinton,[2] in a review on "Trifluoromethylations and Related Reactions in Organic Chemistry" reported a few compounds which are relevant here, namely some trifluoromethylimidazoles which will be discussed in section **I.2.** The reactivity of fluorine-containing β-diketones towards hydrazine (formation of pyrazoles) and hydroxylamine (formation of isoxazoles) has been discussed by Postovskii *et al.*[3] The most important account is that of Chambers and Sargent,[4] which deals with polyfluoroheteroaromatic compounds. The main difference between the present review and that of Chambers and Sargent, besides the references after 1980, is that Chambers and Sargent describe five and six membered heteroaromatic compounds while our review is devoted to five membered compounds with more than one heteroatom but including non aromatic derivatives. Recently,[5] a review on "Recent Advances in Fluoroheterocyclic Chemistry" has appeared which is devoted to six-membered rings; the synthesis of fluorine-containing (i.e., both C-F and C-CF_3) five-membered rings is only briefly described there since a review on this last topic has been published after this manuscript was submitted.[6]

The review will cover CF_3 and C_nF_{2n+1} derivatives of five-membered heterocycles containing at least two heteroatoms, *i.e.* a F-C(sp^3)-heterocyclic bond must always be present [this excludes substituents like $CH(CF_3)_2$ and C_6F_5]. Five-membered rings with one O, S or N Atom, *i.e.* pyrroles and their benzo derivatives, furans and their benzo derivatives, thiophenes and their benzo derivatives will not be considered. In the case of benzazoles only those with the CF_3 group on the five-membered ring are within the scope of this review, *i.e.* compound **1** but not compound **2.** We will follow the same order as in Comprehensive Heterocyclic Chemistry.[7] Within each chapter, the results will be

discussed in the following order: i) structure (theoretical methods, structural methods, tautomerism); ii) reactivity, iii) syntheses and iv) applications.

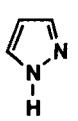


1

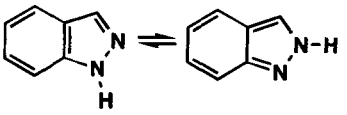


2

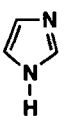
I. FIVE-MEMBERED RINGS WITH TWO OR MORE NITROGEN ATOMS



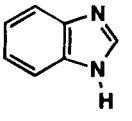
Pyrazole



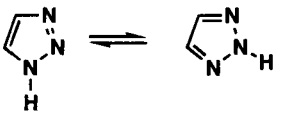
1*H*-Indazole 2*H*-Indazole



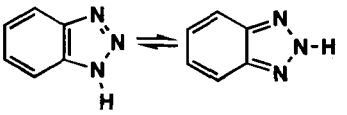
Imidazole



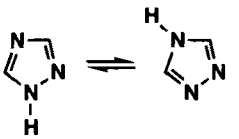
Benzimidazole



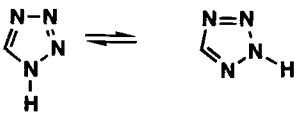
1*H*-1,2,3-Triazole 2*H*-1,2,3-Triazole



1*H*-Benzotriazole 2*H*-Benzotriazole



1*H*-1,2,4-Triazole 4*H*-1,2,4-Triazole

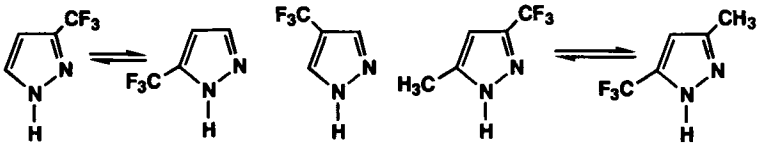


1*H*-Tetrazole 2*H*-Tetrazole

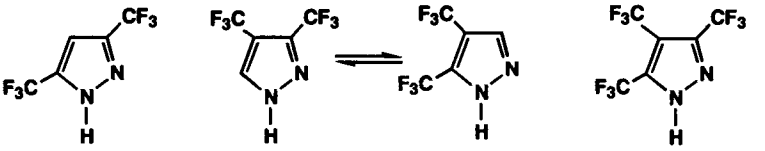
1. Pyrazoles and their Benzo Derivatives

(i) Structure

Theoretical calculations at the *ab initio* level on simple trifluoromethylpyrazoles have been carried out.[8,9] Mass spectrometry studies of pyrazoles including trifluoromethyl derivatives have been reported[10,11] as well as on Δ^1- and Δ^2-trifluoromethylpyrazolines.[12] Although the most important results concerning ^{19}F and ^{13}C nmr spectroscopy of these compounds will be summarized in §**III.1.**i and **III.2.**i, the main references are quoted here for pyrazoles (including ^1H nmr), pyrazolines and pyrazolinones.[13-21] Other structural studies include acid-base properties of trifluoromethylpyrazoles in the gas phase,[22] the electron diffraction structure of 3,5-*bis*(trifluoromethyl)pyrazole **6**,[9] as well as the HOMO-LUMO and log P of 3-hydroxy-4-amino-5-trifluoromethylpyrazole.[23] The rearrangement of the trimethylsilyl group in the 1-trimethylsilyl derivative of **6** has been studied by ^1H and ^{19}F nmr spectroscopy.[24]

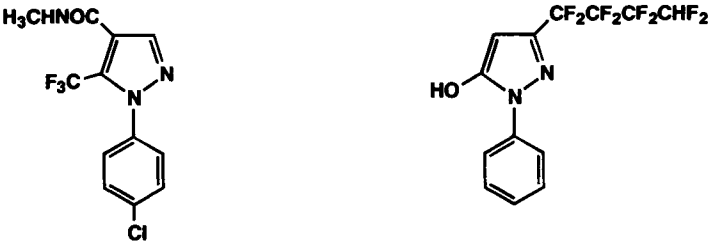


3a 3b 4 5a 5b



6 7a 7b 8

The tautomerism **5a/5b** has been discussed in detail,[17] the authors favor tautomer **5a**. The X-ray structures of 1-(4-chlorophenyl)-*N*-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide **9**[25] and 1-phenyl-3-H$(CF_2)_4$-5-hydroxypyrazole **10** have been reported.[26]



9 10

(ii) Reactivity

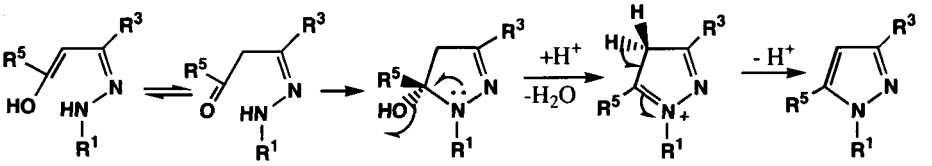
When there is only one CF_3 group present in the ring, trifluoromethylpyrazoles behave like other pyrazoles and, for instance, bromination at position 4 as well as transformation of pyrazolones into 5-bromopyrazoles has been reported.[13] However, 3,5-*bis*(trifluoromethyl)pyrazole **6** cannot be nitrated at the 4 position.[27] Interest in trifluoromethylpyrazoles was recognized early by Trofimenko who prepared the corresponding pyrazaboles.[28] Other trifluoromethylpyrazoles, like **5**, were used to prepare platinum complexes and the X-ray structures of the resulting complexes were reported.[17]

Trifluoromethylpyrazoles were used as starting materials for the synthesis of pyrazolo[1,5-*a*]pyrimidines.[29] A theoretical and experimental study of the FVP (Flash Vacuum Pyrolysis) of trifluoromethylpyrazoles has been published.[8] Decomposition of Δ^1- and Δ^2-pyrazolines carrying five trifluoromethyl substituents have been used to prepare strained vinylcyclopropenes.[30]

(iii) Syntheses

3(5)-Trifluoromethylpyrazoles were prepared using the same methods as with conventional pyrazoles,[7] the main difference being that the intermediate 5-hydroxypyrazolines **12** are usually isolated. According to the mechanism proposed for the formation of pyrazoles by reaction of β-dicar-

bonyl compounds with hydrazines,[31] the presence of a strong electron-withdrawing substituent at position 5 hinders the formation of the intermediate immonium salt **13**. Other authors have also isolated the 5-hydroxy-5-R_F-Δ^2-pyrazolines **12**. [32-35] The last authors reported that for $R^1 = C_6H_5$, the dehydration of **12** to get **14** using sulfuric acid failed.[35]



11a **11b** **12** **13** **14**

The spectroscopic results indicate that in the case $R^5 = CF_3$, the 5-hydroxypyrazoline exists as **12** and not in the open-chain tautomer **11** (the monohydrazone of the β-diketone).[36] In some cases, when R^1 is an electron-withdrawing group, such as $CSNH_2$, the enol **11a** was isolated.[37] The same authors reported the transformation **12** → **14** in the case of 3(5),4-polymethylene-5(3)-trifluoromethylpyrazoles.[37] In the synthesis of 3-hydroxy-5-trifluoromethylpyrazoles the intermediate 5-hydroxy-5-trifluoromethylpyrazolidinones have also been isolated.[19]

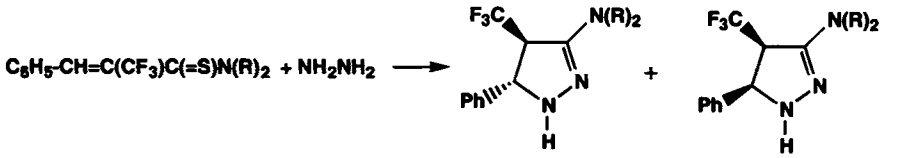
Portnoy reports that the reaction of heterocyclic hydrazines with trifluoromethylated β-diketones of general formulae R^5-CO-CH_2-CO-CF_3 yields only 3-trifluoromethyl derivatives **12** (R^3 = CF_3, $R^5 = CH_3$, C_6H_5);[38] although he gives no proof of this assertion, the structures are probably right. Other authors reported the formation of both possible isomers.[39] The synthesis of trifluoromethylpyrazoles from hexafluoroacetylacetone and hydrazines R-NH-NH_2 (R = H, benzyl, phenyl, *p*-nitrophenyl, 2,4-dinitrophenyl)[40] has been questioned (see below). In the case of R = *p*-chlorophenyl, the pyrazolic structure of the resulting products was established by X-ray crystallography (in this way, compound **9** was prepared).[25] The use of heterocyclic hydrazines has been studied and it has been found that they behave like aromatic hydrazines.[41,42] The problem of establishing, using solely ^{19}F nmr spectroscopy, the structure **12** or **14** of the products obtained has been clarified definitely by Threadgill *et al.*[43] and by Singh *et al.*[44] (see § **III.1.**ii). Regioselective synthesis of trifluoromethylpyrazoles by selective protection of trifluoromethyl-β-diketones has been achieved.[33,42,45]

Ethyl (trifluoromethyl)acetoacetate has been used to synthesize 3-trifluoromethylpyrazolin-5-one, a useful precursor of acetylenic esters.[16] Other authors have successfully used the reaction of hydrazines with trifluoroacetylacetylenes and with acetylenic esters to prepare trifluoromethyl-pyrazoles and pyrazolinones.[32,46] Reaction of copper(II) polyfluorinated β-diketones and β-keto-esters with hydrazines yields the corresponding trifluoromethyl-pyrazoles and pyrazolinones.[21,26] The same kind of compounds can be prepared from β-trifluoroacetyl-lactams.[47] Other functional derivatives of β-diketones have been used to prepare 3(5)-fluoroalkyl-ethoxycarbonylpyrazoles.[48] Trifluoromethylpyrazolinones have been prepared starting from acetylenic esters and from haloalkyl-substituted α,β-unsaturated esters; in both cases the modification of the 3-OH/5-OH isomer ratio, with

regard to that obtained using β-ketoesters, was the main purpose.[21,49] Finally, reaction between phenylhydrazine and the trifluoromethylated analogue of benzylideneacetone yields 1,3-diphenyl-5-trifluoromethyl-Δ^2-pyrazoline[21] and not the isomeric 1,5-diphenyl-3-trifluoromethyl-Δ^2-pyrazoline as was reported previously.

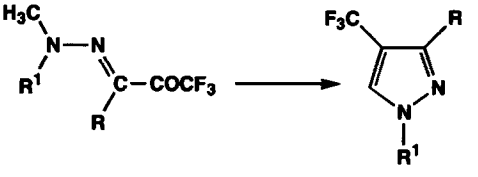
Apart from the general reaction between hydrazines and β-diketones (pyrazoles), β-ketoesters (pyrazolinones) and α,β-unsaturated ketones (pyrazolines), other methods have been extensively used for the synthesis of trifluoromethylated derivatives of pyrazoles, pyrazolinones and pyrazolines.

The problem of the synthesis of 4-trifluoromethyl derivatives of pyrazoles has been thoroughly discussed by Meazza *et al.*[50] and a new and general method has been described. Other less general syntheses had been reported previously,[51-56] as well as formation of 3-dialkylamino-4-trifluoromethylpyrazoles from trifluoropyruvic thioamides.[57,58]. α-Trifluoromethyl thiocinnamides react with hydrazine to yield a mixture of *trans*- and *cis*-Δ^2-pyrazolines;[58] the *cis*-isomers **16** are predominant, probably due to the protonation of the intermediate Δ^3-pyrazoline by the less hindered face,[59] these pyrazolines are readily oxidized to the corresponding pyrazoles.[58] The X-ray structure of the *trans* pyrazoline **15** is reported in the same paper.



15 **16**

A series of methods makes use of the N-N bond of hydrazones and azines. Thus, the 'criss-cross' cycloaddition of hexafluoroacetoneazine with acetylenic compounds yields a zwitterion which rearranges into a 3-trifluoromethylpyrazole[60] or condenses with another triple bond to yield pyrazolo[1,2-*a*]pyrazole derivatives.[14] In some cases Δ^3-pyrazolines are formed which eliminate trifluoroethene to yield 3-trifluoromethylpyrazoles.[15] Benzo[*g*]indazoles were prepared by N-N exchange reaction of *N,N*,-dimethyl-2,4-*bis*(trifluoroacetyl)-1-naphthylamine **64** (§ **II.1.**iii) with hydrazines R^1-NH-NH_2 (R^1 = Me, *t*-Bu, phenyl, 4-nitrophenyl).[61] The very interesting synthesis of pyrazoles **17**



17

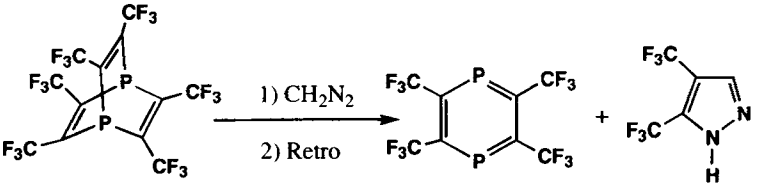
from hydrazones has the limitation that position 5 has to remain unsubstituted.[62,63] Aldehyde methylhydrazones react with ethyl β-trifluoro-acetylvinyl ether to afford intermediate enamino-

hydrazones which can be cyclized by trifluoroacetic acid; in this way, 1-methyl-3-trifluoromethylpyrazole was prepared.[64]

Other methods use the N-N bond of diazo compounds; the CF_3 groups are provided either by the diazocompound (*i.e.* trifluorodiazoethane) or by the olefinic or acetylenic derivative (*i.e.* hexafluorobutyne). The main paper in this regard is that of Atherton and Fields.[13] These authors used 2,2,2-trifluorodiazoethane and a variety of olefines and acetylenic compounds (including CF_3 substituted derivatives) to prepare Δ^1-pyrazolines, *cis* and *trans* Δ^2-pyrazolines and trifluoromethylpyrazoles, for instance **3**, **6**, **7**, and **8** (for this last compound, see also ref. 65).[13] 1,3-Dipolar cycloaddition of diazomethane to trifluoromethyl-substituted alkenes allows the synthesis of trifuoromethyl Δ^1- and Δ^2-pyrazolines.[66] α-Trifluorodiazo compounds have been used to prepare 3(5)-trifluoromethyl-5(3)-phenylpyrazole.[18] Trifluoro-methylacetylacetylenes are reported to give 4-trifluoromethylpyrazoles in good yields.[67] The reaction of diazocyclopentadienes with hexafluoro-2-butyne yields trifluoromethyl derivatives of spiropyrazolenines.[68] Nitrile imines, prepared from hydrazonyl halides, react with β-perfluoroalkyl-β-dicarbonyl compounds to afford 4-acyl-5-perfluoroalkylpyrazoles.[69] 3(5)-Trifluoromethylpyrazole **3** has been prepared, in a quantitative yield, from 2-bromotrifluoropropene and diazomethane.[70] This procedure is a great improvement over that of Fields and Tomlinson.[64] The Chinese authors have prepared 3(5)-trifluoromethyl-5(3)-methylpyrazole **5** from **3** by electrophilic substitution on the lithio derivative of 1-pyrrolidinomethyl-3-trifluoro-methylpyrazole.

Trifluoromethylpyrazoles have also been prepared from other heterocycles. Thus, *bis*(trifluoromethyl)spiropyrazolenines can be transformed into pyrazolo-pyridines and 3*H*-indazoles.[68] Trifluoromethylpyrazoles have also been obtained from 1*H*-Δ^3-pyrazolines.[15,71] 3,4-Bis(trifluoromethyl)-1-phosphorylpyrazoles have been prepared by rearrangement of the corresponding pyrazolenines.[72]

An interesting reaction is the obtention (in quantitative yield) of 3(5),4-*bis*(trifluoromethyl)-pyrazole **7** as a secondary product from compound **18**.[73-75]



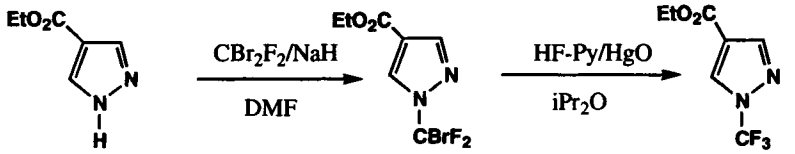
18 **7**

The [4+1] cycloaddition of 3,6-*bis*(trifluoromethyl)-1,2,4,5-tetrazine with isocyanides yields, in two steps, the interesting 3,5-*bis*(trifluoromethyl)-4-aminopyrazole.[76] Dihydroindazoles have been prepared by the same authors from 3,6-*bis*(trifluoromethyl)-1,2,4,5-tetrazine by a Diels-Alder reaction with inverse electron demand.[77]

Finally, some important compounds have been prepared using miscellaneous methods. Thus, the synthesis of trifluoromethyl substituted pyrazoles from 1,1,1-trifluoro-3-phenylsulfonyl-2,2-

propanediol has been reported.[78] A novel and practical method for preparing 3-trifluoromethylpyrazoles used as starting material perfluoroiodopropane and acetylenic compounds.[79] 1-Methyl-3-perfluoroalkyl-4-fluoro-5-phenylpyrazoles have been prepared from 1-phenyl-1-trimethylsilyl perfluoroalkanols,[80] a rather complex reaction but one which proceeds in excellent yields (the same compounds can also be obtained from enol phosphate derived from perfluoroalkyl ketones).[81] The reaction of α,α,α-trifluorotoluene, hydrazine and ozone was reported to give a mixture of several products, amongst them 3(5)-trifluoromethylpyrazole **3** and 4-trifluoromethylpyrazole **4** but without any structural proof.[82]

One of the rare examples of a trifluoromethylazole substituted on the nitrogen **20** has been reported by Morimoto *at al.*[20] The sequence represented below has been used.

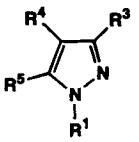


19 **20**

Two simple trifluoromethylpyrazoles have been described several times and in most cases as if they were new compounds not quoting the previous references. Moreover, in some cases quite different melting points were reported. This is the case of 3(5)-trifluoromethyl-5(3)-methylpyrazole **5**: mp 89-90°,[10] described as unknown but no mp reported,[17] mp 87-88°,[22] mp 85-86°,[64] mp 84-85°,[70] mp 102-104°.[83] Concerning 3,5-*bis*(trifluoromethyl)pyrazole **6**: mp 84°,[28] mp 83-84°,[22] mp 57-60°,[13] mp 71-72°,[40] mp 69-70°,[43] mp 70-75°,[84] (see also ref. 40), mp 68-70°.[24]

Table 1 reports trifluoromethylpyrazoles which are commercial products (from the "Available Chemical Directory" of Chemical Design).

TABLE 1. List of Commercially Available Pyrazoles

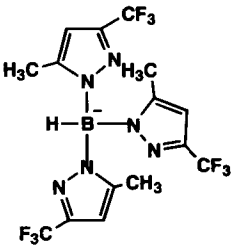


No	R^1	R^3	R^4	R^5	No	R^1	R^3	R^4	R^5
21	H	H	CO_2Et	CF_3	**28**	C_6H_5	H	CO_2Et	CF_3
22	CH_3	*a*	H	CF_3	**29**	C_6H_5	H	COCl	CF_3
23	CH_3	*b*	H	CF_3	**30**	C_6H_5	H	$CONHNH_2$	CF_3
24	CH_3	CF_3	H	*b*	**31**	*p*-ClC_6H_4	H	CO_2Et	CF_3
25	CH_3	CF_3	H	*c*	**32**	*p*-ClC_6H_4	H	CO_2H	CF_3
26	CH_3	*c*	H	CF_3	**33**	*p*-ClC_6H_4	H	COCl	CF_3
27	CH_3	CF_3	CHO	Cl	**34**	*p*-ClC_6H_4	H	$CONHNH_2$	CF_3

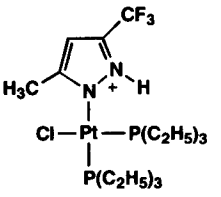
a) 3,5-*bis*(sulphonylchloride)thiophen-2-yl. b) 5-(carboxaldehyde)thiophen-2-yl. c) 5-(carboxylchloride)thiophen-2-yl.

(iv) Applications

The ligand tris[3-trifluoromethyl-5-methyl(pyrazol-1-yl)]borate **35** yields a hydridovinyl iridium complex more stable than its η^2-ethylene isomer.[85] The X-ray structure of the related platinum complex **36** has been described.[17]

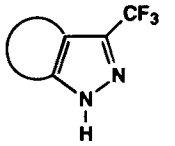


35



36

Amongst the various biological activities described for perfluoroakylpyrazoles are: growth inhibitory activity of derivatives of *N*-trifluoromethylpyrazoles **20**,[20] high biological activity as herbicides,[21,86] fungicides,[87] insecticides,[88] and as analgesic, antipyretic, anti-inflammatory and hyperglycemic agents.[50] A series of patents by Monsanto Co. described the herbicidal properties of 3(5)-aryloxy-5(3)-trifluoro-methylpyrazoles[89,90] as well as those of 3(5)-aryl-5(3)-trifluoromethylpyrazoles.[91] *N*-Sulfonyl-3,5-*bis*-(trifluoromethylpyrazole) has hyperglycemic activity.[84] Other compounds with analgesic, antipyretic and antiinflammatory properties are the 1,5-diaryl-3-trifluoromethyl- and 1,3-diaryl-5-trifluoromethylpyrazoles.[39] On the other hand, polymethylene derivatives **37** lack any activity.[37]

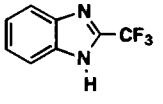


37

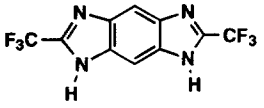
2. Imidazoles and their Benzo Derivatives

(i) Structure

Although the ^{19}F and ^{13}C nmr spectroscopy of these compounds will be discussed later (§ **III.1**.iii and **III.2**.iii) there are some relevant references for ^{1}H nmr,[92] for ^{19}F nmr,[93,94] and for ^{13}C nmr.[95] Slow prototropic annular tautomerism of 2-perfluoropropyl- and higher 2-perfluoroalkyl-NH-imidazoles was assigned to intramolecular N-H···F hydrogen bonds.[94] A series of papers by Ogretir and Demiyarak deals with acid-base properties, kinetics of nitration and Hammett relationships of a series of benzimidazoles including 2-trifluoromethylbenzimidazole **1**, 2-trifluoromethyl-5-nitrobenzimidazole and related compounds, like **38**.[96-101] For instance, the pK_a's of compound **1** are 1.97 (proton-gain, *i.e.* basicity) and 8.13 (proton-loss, *i.e.* acidity).



1



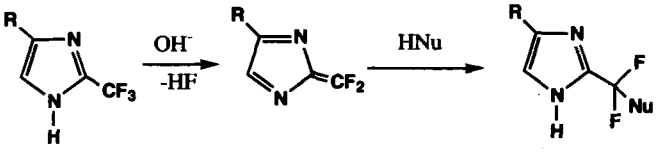
38

An absorptimetric and fluorimetric study of solvent dependence on the absorption and fluorescence spectra as well as on the acidity and the basicity of 2-trifluoromethylbenzimidazole **1** in the

ground as well as in the excited state has been published [absorption maxima in methanol, λ/nm; log ε: 283 (3.78), 275 (4.03), 268 (3.98), 254 (4.00)].[102] Finally, the partition coefficient of **38** has been determined.[103]

(ii) Reactivity

A general property of ring-trifluoromethylated imidazoles **39** at positions 2 or 4(5) is the tendency to eliminate hydrogen fluoride under rather mild alkaline conditions to form transient difluorodiazafulvenes **40**;[104] the latter species have been found to react rapidly with a variety of nucleophiles to yield imidazoles **41**, ultimately providing additional analogues of histamine and histidine.[105] The transformation of trifluoromethyl groups, for instance that of compound **39**, into CO_2H has been reported; the reaction proceeds through **41** and 2-(trihydroxymethyl)imidazole.[104] A related reaction is the condensation of **1** with *o*-phenylenediamine to yield 2,2'-bibenzimidazole.[1] Nucleophilic substitution of the C_5-F atom in 5-fluoro-4-trifluoromethylimidazoles yields a variety of 5-substituted imidazoles without affecting the CF_3 substituent.[106]

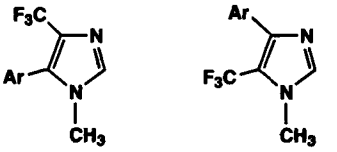


39 **40** **41**

Nitration kinetic studies of 2-trifluoromethylbenzimidazole **1**,[96] as well as its bromination,[107] have been published.

(iii) Syntheses

A series of 2-trifluoromethylimidazoles, including histamine and L-histidine-like derivatives has been described[108] as well as the photochemical perfluoroalkylation of imidazoles;[94] photochemical trifluoromethylation of some biologically significant imidazoles (histamines, histidines);[105,109] (see also ref. 110); 4-CF_3-5-F-imidazoles;[111] regioselective introduction of CF_3 groups has also been reported.[112,113] In ref. 2 several references concerning the preparation of trifluoromethylimidazoles are quoted.[94,104,105,109,110] Fluoroalkylation of imidazole anion with perfluoroalkyl iodides or bromides provided an easy entry to 4(5)-fluoro-alkylimidazoles [for instance, $R_F = (CF_2)_4CF_3$].[114] 2-Substituted-4(5)-trifluoromethyl-imidazoles (R = H, alkyl, aryl or heteroaryl) have been prepared by treating CF_3COCHX_2 (X = halo) with a base and then with ammonia and a carboxaldehyde RCHO.[115] The use of trifluoroacetylated dimethylhydrazones for the selective synthesis of one regioisomer of 4- and 5-trifluoromethylimidazoles **42** and **43** has been reported.[92,116] In a similar way, the corresponding N-H derivative has also been prepared by Kamitori *et al.*[117]



42 **43**

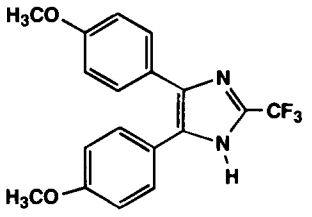
2- and 4-Perfluoroalkylimidazoles (including trifluoromethyl) have been prepared by electrochemically induced $S_{RN}1$ substitution.[118] 2-Trifluoromethyl-imidazole and 2,4,5-tris(trifluo-

romethyl)imidazole were prepared by treating the corresponding carboxylic acids by SF_4.[93]

Concerning benzimidazoles and related compounds, they have been prepared by reacting *o*-phenylenediamines (or related heterocyclic derivatives) with trifluoro-acetic acid; in this way compound **1** and 2,6-*bis*(trifluoromethyl)1*H*-imidazo[4,5-*b*]pyridine have been prepared.[119,120] Instead of trifluoroacetic acid, hexafluoro-acetylacetone or related dicarbonyl compounds have been used to prepare **1** and other 2-R_F-benzimidazoles.[48,121] Trifluoromethylation of 8-haloadenosine and inosine with trifluoromethyl-copper complex yields the corresponding 8-CF_3 derivatives.[122] From compound **1** several 1-substituted derivatives were prepared by *N*-alkylation, including acyclic analogs of nucleosides[123] and ribofuranosides.[124] Finally, 2-R_F-imidazolines, with R_F = CF_3 and C_3F_7, were prepared from perfluoroacetamidate and perfluorobutyrimidate and ethylenediamine.[125]

(iv) Applications

The biological properties of 4-trifluoromethylimidazoles as xanthine oxidase inhibitors[126] and as peripheral vasodilator β-adrenergic blocking agents have been described.[127] 2-Trifluoromethylbenzimidazole **1** shows growth-inhibitory effects,[98] as well as tryptophan synthase inhibition.[128] The antiinflammatory activities of 2-trifluoromethyl-4,5-diarylimidazoles have been reported; for instance, the 4-methoxyphenyl derivative, *Flumizole*, is more potent than indomethacin.[129] 2-Trifluoromethylbenzimidazole ribofuranosides with antiviral activity have been described.[124]

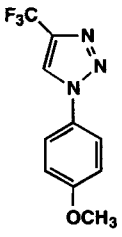


Flumizole

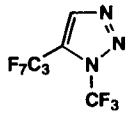
3. 1,2,3-Triazoles and their Benzo Derivatives

(i) Structure

The ^{13}C and ^{19}F nmr spectroscopy of 1-methyl-4-trifluoromethyl-1,2,3-triazoles and 1-methyl-5-trifluoromethyl-1,2,3-triazoles as well as the X-ray structure of 1-(*p*-methoxyphenyl)-4-trifluoromethyl-1,2,3-triazole **44** have been reported.[130] There is some information about the ^{19}F nmr spectroscopy of 1,2,3-triazolines[131] (see also § **III.1.**iv).



44



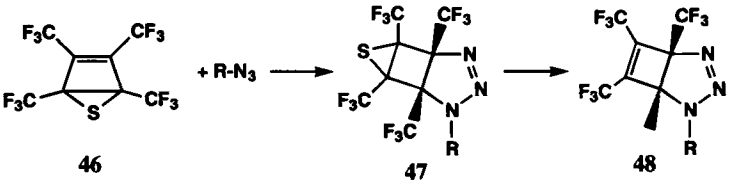
45

(ii) Reactivity

Irradiation of 1-phenyl-4,5-*bis*(trifluoromethyl)-1,2,3-triazole affords 2,3-*bis*(trifluoromethyl)indole **60** (see § **II.1**).[76]

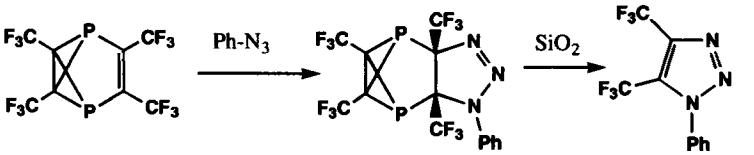
(iii) Syntheses

One of the rare *N*-CF_3 azoles **45** was obtained by reaction of diazomethane on $CF_3N{=}CFC_3F_7$.[132] The reaction of diazomethane with perfluoroimines also yields perfluoroalkyltriazoles.[132,133] 1-Substituted-1,2,3-triazoles bearing a trifluoromethyl substituent at position 4 or 5 have been obtained by cycloaddition of organic azides with trifluoromethylacetylenes.[130] Bicyclic compounds **47** and **48** were obtained by reaction of several azides R-N_3 (R = H, C_6H_5, C_6H_{11}, *t*-C_4H_9) with tetra(trifluoromethyl)-Dewar thiophene **46**.[131] The phosphorus derivative **18** and phenylazide yielded the corresponding triazoles.[76]



46 **47** **48**

1-Phenyl-4,5-*bis*(trifluoromethyl)-1,2,3-triazole **49** has been prepared by the following sequence of reactions:[134]

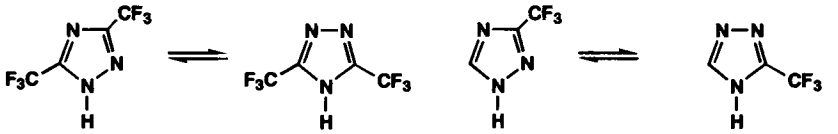


49

4. 1,2,4-Triazoles

(i) Structure

^{19}F Nmr and ^{13}C nmr spectra of trifluoromethyl-1,2,4-triazoles have been described[135-137] (see also § **III.1.**iv). The structure, gas-phase basicity and thermodynamic properties of 3,5-*bis*(trifluoromethyl)-1,2,4-triazole **50** have been studied; high level *ab initio* calculations (MP2/6-31G*) of compound **50** together with those of the monosubstituted derivative **51** have been carried out;[138] concerning tautomerism, 1*H*-tautomers, **50a** and **51a**, are always the most stables. The pK_a (proton-gain, *i.e.* basicity) of some trifluoromethyl-1,2,4-triazoles have been measured.[139]



50a **50b** **51a** **51b**

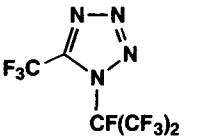
(ii) Reactivity

Reaction of **50** with ethyl propynoate and of its sodium salt with ethyl bromoethanoate and pentafluoropyridine yield the acrylate-, carboethoxymethyl- and fluoropyridyl-derivatives of 1*H*-3,5-*bis*(trifluoromethyl)-1,2,4-triazole.[137]

(iii) Syntheses

3,5-Bis(perfluoroalkyl)-1,2,4-triazoles have been prepared by two general methods: a) from perfluoroalkylcarboxylic acids or their derivatives (perfluoro-alkylnitriles, perfluoroalkylimidates) and hydrazines;[125,140,141] b) from 3,5-*bis*(perfluoroalkyl)-1,3,4-oxadiazoles (§ **II.5**) and ammonia (N-H), primary amines (N_4-R) and hydrazine (N_4-amino).[136,139,140,142,143] The mechanism of the last procedure has been carefuly studied.[136] For both methods, an intermediate dihydrotetrazine can be isolated in some cases.[140] The synthesis of 1-methyl-3,5-*bis*(trifluoromethyl)-1,2,4-triazole has been described.[144] The reaction between 1,4-*bis*(trifluoromethyl)-1,2,4,5-tetrazine and dimethylaminocycloheptatriene affords imines derived from 4-amino-3,5-*bis*(trifluoromethyl)-1,2,4-triazole.[137]

5. Tetrazoles



52

(i) Structure

Compound **52** is one of the rare *N*-perfluoroalkyl azoles that has been described.[145] The X-ray structure of the [(trifluoromethyl-tetrazole)$_3$Mn$_2$(CO)$_6$]$^-$ anion has been reported[146] as have the ^{13}C and ^{15}N nmr spectra of trifluoromethyl-tetrazolate anion.[147] In this last reference, the ^{15}N chemical shifts of a Co(III) complex of trifluoromethyltetrazole are also reported.

(ii) Reactivity

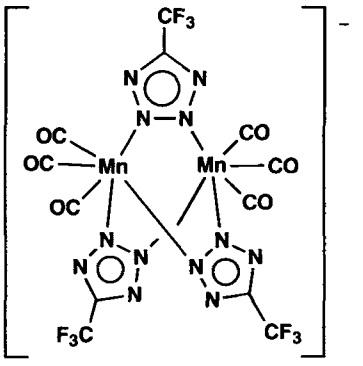
Transformation of trifluoromethyltetrazole into trifluoromethyl-1,3,4-oxadiazoles has been accomplished (see § **II.5**).[148] The reactivity of trifluoromethyltetrazole with 2-nitro-2-azapropanol has been investigated[149] so has the selective N-2 alkylation of 5-trifluoromethyltetrazole by alcohols in conc. H_2SO_4.[150] Moreover, 5-trifluoro-methyltetrazole has electrophilic properties and readily underwent addition reactions with vinyl ethers or arylacetylenes.[151]

(iii) Syntheses

Perfluoroalkylated tetrazoles are readily prepared either using fluorinated nitriles and alkali azides[1,152] or by reaction of trimethylsilylazide with such imines as $CF_3CCl{=}NCF(CF_3)_2$.[145]

(iv) Applications

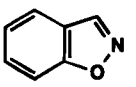
5-Perfluoroalkyltetrazoles are useful η^5 ligands in solution and μ-2,3-η^5 ligands in solid manganese complexes;[146] the X-ray structure of complex **53** is illustrated here.



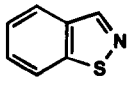
53

II. FIVE-MEMBERED RINGS WITH TWO OR MORE OXYGEN, SULFUR OR NITROGEN ATOMS.


Isoxazole

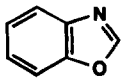

Benzisoxazole


Isothiazole

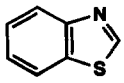

Benzisothiazole


1,2,4-Oxadiazole


Oxazole


Benzoxazole


Thiazole


Benzothiazole


1,3,4-Oxadiazole


1,2,5-Oxadiazole


1,2,4-Thiadiazole


1,3,4-Thiadiazole

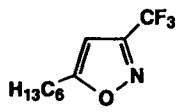

1,2,5-Thiadiazole

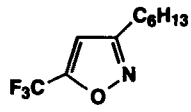

1,2,3,4-Thiatriazole

1. Isoxazoles and their Benzo Derivatives

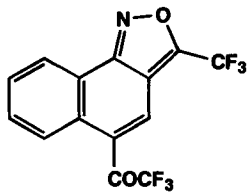
(i) Structure

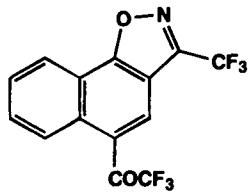
Generally the structures of isoxazoles were determined on the basis of their ^{1}H and ^{13}C nmr data as well as their ^{19}F nmr spectra (§ **III.1**.v). The regioisomeric isoxazoles **54** and **55**, described by Linderman *et al.* are distinguishable by ^{19}F nmr spectroscopy.[32] The trifluoromethyl signals appeared at -64 and -65 ppm for **54** and **55** respectively. Other ^{19}F chemical shifts of isoxazoles are reported for a pentafluoroethyl derivative.[153]


54


55

The structures of two isomers of benzoisoxazole **56** and **57**, reported in a work of Hojo *et al.*, could be differentiated on the basis of the ^{13}C nmr spectra.[61] The nitrogen-substituted carbon of **56** appears at 155.6 ppm while the oxygen-substituted carbon of **57** gives a signal at 165.0 ppm.

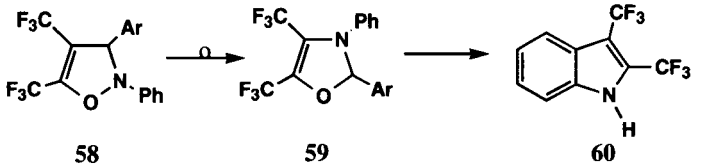

56


57

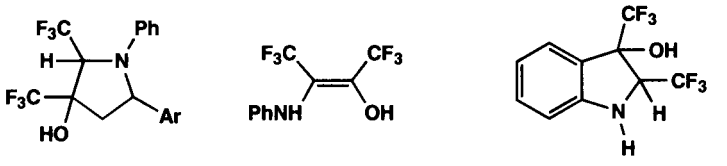
(ii) Reactivity

Few authors have described the reactivity of trifluoromethylisoxazoles. Here we are reporting two reactions, a rearrangement of an isoxazoline and a ring opening reaction of an isoxazole. First, Δ^4-isoxazolines **58** could be rearranged into Δ^4-oxazolines **59**.[154] Second, hydrolysis followed by

cyclization of **59** gave the *bis*(trifluoromethyl)indole **60**; three intermediates, a hydroxyoxazoline (**A**) an enamine (**B**) and a hydroxyindoline (**C**), precursors of **60** were isolated.



58 **59** **60**

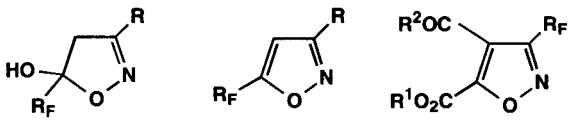


A **B** **C**

5-Trifluoromethylisoxazole may be ring-opened to enolates of 3-oxo-4,4,4-trihalobutylnitriles, which are useful as halogenated C_3 synthons.[155]

(ii) Syntheses

5-Trifluoromethylisoxazoles could be obtained by chlorine-fluorine exchange reactions from easily accessible 5-trichloromethylisoxazoles.[155] Nevertheless, trifluoromethyl-isoxazoles are usually synthesized through cyclization of a properly functionalized trifluoromethylaliphatic precursor. Trifluoromethyl substituted isoxazoles **54** and **55** have been prepared by reaction of hydroxylamine on trifluoro-acetylacetylene. The regioselectivity of this addition could be controlled by the choice of the reaction conditions.[32] 5-Trifluoromethylisoxazoles **62** were also synthesized from trifluoromethyl β-diketones and hydroxylamine.[156,157] The regioselectivity of this cyclization is due to the fact that the trifluoromethyl group shifts the keto-enol equilibrium of the β-diketones towards the enol form of the trifluoromethyl substituted carbon. It is interesting to note that the dehydration of the intermediate 5-hydroxy-5-perfluoroalkyl Δ^2-isoxazolines **61** occurred in refluxing benzene in the case of the trifluoromethyl Δ^2-isoxazoline,[32] and in polyphosphoric acid at 180-200° in the case of the perfluoroalkyl Δ^2-isoxazoline,[156,157] while 5-alkylisoxazolines lose water spontaneously. Starting from trifluoroacetylated enol ethers and hydroxylamine, dihydro derivatives **61** ($R_F = CF_3$) were isolated as stable compounds.[158]

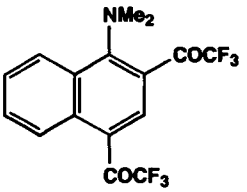


61 **62** **63**

Resnati *et al.* have reported a regioselective synthesis of 5-trifluoromethylisoxazoles.[159] By reacting the triethylammonium salts of β-trifluoroalkyl-β-ketoesters with nitrile oxides, the corresponding isoxazolines were formed in good yield and their dehydration took place very easily to give the 4-carbonyl substituted derivative of the oxazole **62**.[159] Reaction of nitrile oxides, prepared from

halooximes, with β-perfluoroalkyl-β-dicarbonyl compounds afford 4-acyl-5-perfluoroalkylisoxazoles.[69] A synthesis of 5-trifluoromethylisoxazoles has also been described in some reaction studies of amines with perfluoroolefins.[153] 3-Trifluoromethylisoxazole-5-carboxylates **63** were prepared *via* cycloaddition of nitrile oxide with the appropriate β-acylpyruvates in the absence of base.[160] On the other hand, 3-trifluoromethyl-4-aminoisoxazole-5-carboxylates were synthesized by the reaction of the corresponding bromoaldoximes with cyanoacetate.[161]

2,3-Diaryl-4,5-*bis*(trifluoromethyl)-Δ^4-isoxazoline **58**, whose rearrangement has been cited previously (§ **II.1.**ii), was formed from the reaction of nitrones on hexafluorobutyne.[154] As we have reported in the section dealing with benz[*g*]indazoles (§ **I.1.**iii), *N,N*-dimethyl-2,4-*bis*(trifluoroacetyl)-1-naphthylamine **64** undergoes an aromatic nucleophilic N-N exchange reaction with hydrazines to afford the corresponding trifluoromethylated benz[*g*]indazoles. This method has been used successfully for the high yield synthesis of 3-trifluoromethylnaphthisoxazoles **56** (§ **II.1.**i) using hydroxylamine instead of hydrazine. On the other hand, its regioisomer **57** was prepared in low yield starting from 2,4-*bis*(trifluoroacetyl)-1-naphthylamine **65**.[61]



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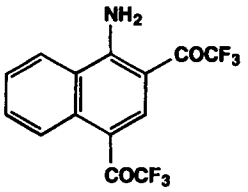


65

(iv) Applications

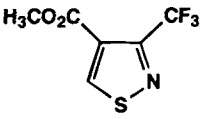
The interest in the biological activities of the trifluoromethylisoxazoles is shown in the following examples. 3-Trifluoromethyl-5-aminoisoxazole derivatives were tested for antiinflammatory activity.[161] A 5-trifluoromethylisoxazole-4-carboxamide belonging to a series of isoxazole-4-carboxamides shows activity as neoplasm inhibitor and antirheumatic.[162] Among a novel series of styrylisoxazoles, which were found to be dual inhibitors of 5-lipoxygenase and cyclooxygenase in rat basophilic leukemia cells, a styryl-trifluoromethylisoxazole has been synthesized.[163] A trifluoromethylisoxazole-carboxamide was reported to be active as herbicide, against broad leaf weeds.[164]

2. Isothiazoles and their Benzo Derivatives

Despite all the work that has been done concerning trifluoromethylated heterocycles few trifluoromethylisothiazoles have been reported.

(i) Structure

The identity of 3- or 5-trifluoromethyl dihalogeno or methoxycarbonyl substituted isothiazoles was established by nmr spectroscopy and mass spectrometry.[165,166] The structure of isomers **66** and **67** has been deduced from mass spectra fragmentation studies. In the isomer **66**, the proximity of the trifluoromethyl and the methoxycarbonyl groups allowed, for the synchronous loss of hydrogen fluoride, while for isomer **67** this fragmentation was not observed.[166]



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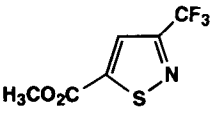
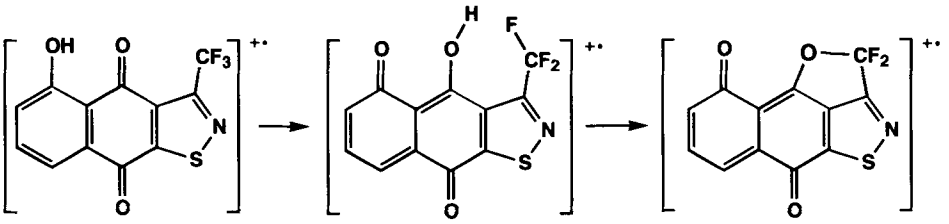


67

By mass spectrometry considerations also, the isothiazolonaphthoquinone **68** has been shown to be the regioisomer formed from the reaction of trifluoroacetonitrile *N*-sulfide and juglone. Only the regioisomer with the hydroxyl and trifluoromethyl groups on the same side of the ring system could lose hydrogen fluoride by the mechanism shown below.[166]



68

(ii) Syntheses

Two different syntheses of isothiazoles have been reported. In the first one trifluoroacetonitrile *N*-sulfide, prepared from trifluoroethylimino sulfur difluoride, reacts with acetylenes to yield a 1:5 mixture of 3-trifluoromethyl 4-and 5- substituted isothiazoles **66** and **67**.[166] The 3-trifluoromethyl 5-hydroxy isothiazole naphtho-quinone **68** has been synthesized by the same way using juglone as acetylenic starting material. In the other synthesis the starting materials, 4-halogeno isothiazole 3- or 5-carboxylic acid, were easily prepared and their fluorination with SF_4 in anhydrous hydrogen fluoride gave the corresponding 3- or 5-trifluoromethylated isothiazoles regiospecifically and in good yield.[165]

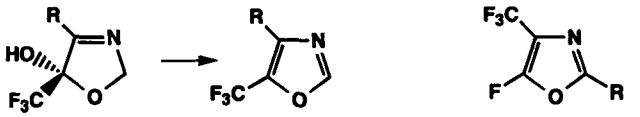
3. Oxazoles and their Benzo Derivatives

(i) Structure

The structure determinations of trifluoromethyloxazoles have mainly been done by ^{1}H, ^{13}C, and ^{19}F nmr spectroscopy.[106,112,167] The structure of 5-trifluoro-4-propanol-2-(1-methyl-2-phenylvinyl)-oxazole has been determined by X-ray crystallography.[168]

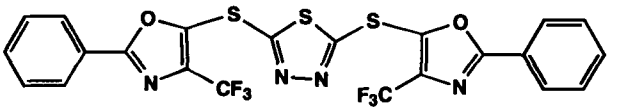
(ii) Reactivity

2-Perfluoroalkyl-Δ^3-oxazolines were found to be unstable and to rearrange slowly at room temperature to *N*-vinylperfluorobutyramide.[125] 5-Trifluoromethyl-Δ^3-oxazolines **69** resisted conventional dehydration reagents and catalysts. A two step conversion, including chlorination and treatment with phosphorus oxychloride in pyridine, followed by a dehydrochlorination with DBU or a tertiary amine, has been performed successfully.[169] Recently the same authors found a more efficient procedure to convert 5-trifluoromethyl-Δ^3-oxazolines **69** to 5-trifluoromethyloxazoles **70** using phosphorus oxychloride at 90°.[170]



69 70 71

By nucleophilic substitution of the fluorine atom, 5-fluoro-4-trifluoromethyl-oxazoles **71**, obtained yielded a wide variety of 5-substituted-4-trifluoromethyl-oxazoles.[106,112,171] With binucleophiles, this substitution has been used for linking trifluoromethyloxazoles to aromatic, heteroaromatic and heterocyclic systems like the bisoxazole **72**.[106]



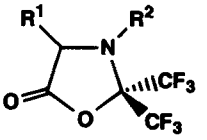
72

5-Azido-4-trifluoromethyloxazoles, obtained by nucleophilic substitution from the corresponding 5-fluorooxazoles **71**, have been shown to be thermolabile and decomposed at room temperature to give the 4-cyano-4-trifluoromethyl-1-oxa-3-azabuta-1,3-dienes.[172] However, a 5-triazoline-4-trifluoromethyloxazole has been isolated and characterized as the [3+2] cycloaddition product of 5-azido-4-trifluoromethyl-oxazole with a carbon-carbon multiple bond system.[173]

5-Amino- or aminomethyl-4-trifluoromethyloxazoles have been prepared from 5-fluorooxazoles.[113] Moreover, reactions of the amino function with electrophiles have been shown to be useful for introducing various side chains of potential biological interest.

Starting also from 5-fluoro-4-trifluoromethyloxazoles **71**, the syntheses of α-trifluoromethyl substituted heteroarylglycine and phenylalanine derivatives have been described.[167] Reaction of 5-fluoro-4-trifluoromethyloxazole with allyl alcohol followed by a Diels-Alder addition yielded trifluoromethyl-β-aminoacid derivatives.[174] 5-Trifluoromethyloxazole-4-ethylester led to a 5-trifluoromethyl-4-amino-3-hydroxy-pyrazole in a two step reaction.[23] 5-Ethoxy-4-trifluoromethyl-2-oxazolecarboxylic acid has been decarboxylated and subsequently used as an aza-diene for the synthesis of trifluoromethyl-pyridinecarboxylic acid from acrylic acid.[175]

Studies of the reactivity of 2,2-*bis*(trifluoromethyl)-oxazolidin-5-ones **73** demonstrated the value of these compounds in amino acid and peptide chemistry. They led to phosphono-, phosphino-, and phosphinyl-sarcosine derivatives *via* a Michaelis-Arbusov reaction,[176] and to oxo-amino acids and heteroaromatic compounds under Friedel-Crafts conditions.[177]

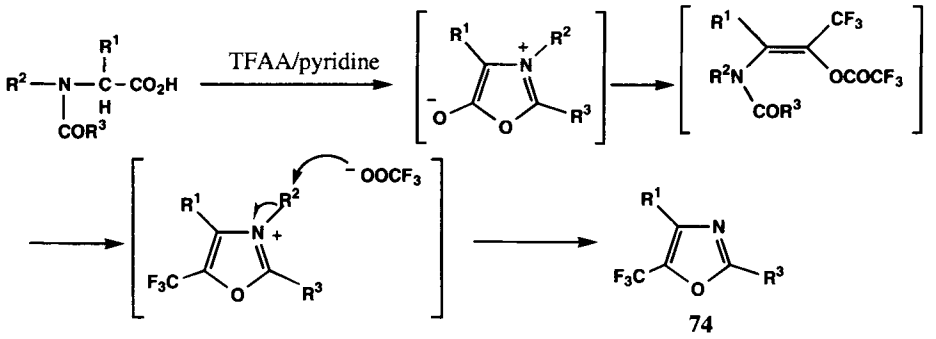


73

(iii) Syntheses

The unexpected formation of 5-trifluoromethyloxazoles **74** by reaction of *N*-acylprolines with trifluoroacetic anhydride under Dakin-West conditions has been reported.[168] This discovery led the authors to find a one-pot synthesis of 5-trifluoromethyl and 5-perfluoroalkyloxazoles from *N*-

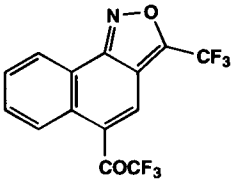
alkyl-*N*-acylamino acids.[178] The following scheme presents the proposed mechanism for the formation of the oxazoles.



74

Thermal cyclization of hydrazono trifluoroalkan-2-ones adsorbed on silica gel afforded the corresponding 5-trifluoromethyl-Δ^3-oxazolines **69**.[169] Therefore the dehydration was achieved in two steps, by chlorination and subsequent dehydrochlorination to give the corresponding oxazole **70**.

4-Trifluoromethyl-5-fluorooxazoles **71** have been synthesized by regioselective reaction of 4,4-*bis*(trifluoromethyl)-1-oxa-3-aza-1,3-butadiene with tin(II)chloride as shown in the following sequence of reactions,[111,112] or with an ultrasound induced procedure in the presence of zinc.[179] This regioselective reaction has been extended to the formation of 1,4-*bis*(2-oxazolyl)benzene **75** from the bifunctional diene, 1,4-*bis*(oxa-3-aza-1,3-diene).[112] More recently, the 2-perfluoroalkyloxazole derivative of **71** has been prepared starting from the perfluorosubstituted butadiene in presence of zinc and a copper salt.[180]



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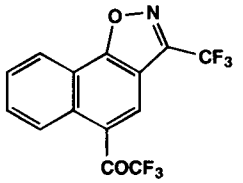

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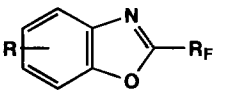
By nucleophilic substitution of the fluorine atom at position 5 of the oxazole **71**, a series of 4-trifluoromethyl-5-substituted oxazoles have been prepared. [106,112,113,171,172] 5-Ethoxy-4-trifluoromethyl-2-oxazolecarboxylic acid has been obtained from ethylcyanoformate and ethyl trifluoroacetyldiazoacetate.[175] Several syntheses of 2-perfluoroalkylated oxazole derivatives have been reported: by reaction of β-azidostyrene with trifluoroacetic acid, 2-trifluoromethyl-5-phenyloxazole was formed;[181] 2-perfluoroalkyl-Δ^2-oxazolines, sufficiently stable to be purified and characterized, have been prepared by cyclization of 2-chloroethyl-perfluoroalkylimidates.[125]

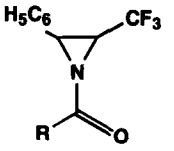
Several benzoxazoles **76** bearing a perfluoroalkyl group in have position 2 been synthesized. Thus, cyclization of substituted 1-hydroxy-2-aminobenzenes with methyl perfluoroalkylacetimidate gave 2-perfluoromethylbenzoxazole.[182] This last compound can also be formed by treatment of the parent benzoxazole with perfluoroalkyl peroxide.[183] The



76

last reaction has also been used for the preparation of perfluoroalkylated oxazoles.

Isomerization of *N*-activated aziridines **77** by sodium iodide, heat, or acid led to five-membered nitrogen heterocycles. In this way, *cis* and *trans* isomers of Δ^2-oxazoline **78** and oxazolidin-2-one **79** have been prepared.[184]



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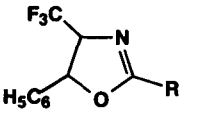

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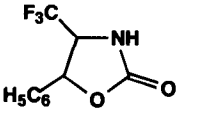


79

The interesting and reactive 2,2-*bis*(trifluoromethyl)-1,3-oxazolidin-5-one **73** can be synthesized by reaction of hexafluoroacetone with a glycine or an amino acid.[176,177,185]

(iv) Applications

Trifluoromethyloxazoles are of interest due to their applications in different fields. Polymers derived from perfluoroalkyloxazolines have been shown to be effective as modifiers of surfaces of hydrophilic polymers,[186] while other polymers derived from heptadecafluoro-decyloxazoles formed polymeric films for second order non-linear optics.[187] Poly(aryl-ether-oxazoles) with trifluoromethyl groups bound to the oxazole moieties, prepared from a bisoxazole monomer, exhibited interesting physical properties.[188]

2-Amino-4,5-disubstituted oxazoles have been tested as herbicide antidotes and the evaluation of some of them has been carried out by comparison with effective herbicides.[189] In the biological area, the interest was focused on oxazole derivatives like 2-trifluoromethyloxazolines, body-membrane penetration enhan-cers[190] or as 2,2-*bis*(trifluoromethyl)-4-(3-diazo-2-oxopropyl)-1,3-oxazolidin-5-ones, useful intermediates for the synthesis of various natural and unnatural α-amino acids.[191]

4. Thiazoles and their Benzo Derivatives

(i) Structure

The ^1H, ^{13}C and ^{19}F nmr data of several 4-trifluoromethylthiazoles have been reported.[106,111,112] (see also § **III.1**.v and **III.2**.iv).

(ii) Reactivity

Nucleophilic substitution of 5-fluoro-4-trifluoromethylthiazoles with phenolate, thiolate and amide ions gave the corresponding substituted compounds in good to satisfying yields.[106] Condensation of 2-aminobenzothiazole with hexafluoroacetone and subsequent treatment with tin(II)chloride yielded 3-fluoro-2-trifluoro-methylimidazo[2,1-*b*]benzothiazole.[112] Two methods have been described to substitute the ring fluorine with amino groups.[192] 5-Aminomethylthiazoles can be obtained by reaction of the corresponding 5-fluoro compounds with potassium cyanide and subsequent reduction,[113] whereas the azido group was introduced by reaction with azides.[172] [3+2] Cycloadditions of 5-azido-4-trifluoromethylthiazoles have also been described.[173]

The thermal stability of photochromic *bis*(trifluoromethylthiazolyl)ethene derivatives was

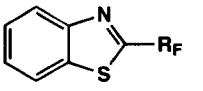
found to increase in comparison with the corresponding methyl derivatives.[193] Several substituted alanines were obtained from aspartic acid *via* 2,2-*bis*(trifluoromethyl)-4-(3-bromo-2-oxopropyl)-1,3-oxazolidin-5-one.[194]

(iii) Syntheses

The reaction of 4,4-*bis*(trifluoromethyl) substituted thiocarboxamides with tin(II)chloride affords 5-fluoro-4-trifluoromethylthiazoles.[111] This sequence was used extensively to obtain the mentioned thiazole as starting material for a great variety of nucleophilic substitutions of the ring fluorine atom.[113,172,173,192]

5-Trifluoromethylthiazoles were obtained from hydrazones in a one-pot-reaction;[170] the intermediate 5-hydroxy-5-trifluoromethyl-Δ^3-thiazolines have been isolated.[117] Fluorination of thiazole carboxylic acids with hydrogen fluoride and sulfur tetrafluoride gave trifluoromethylated thiazoles.[165,195] 2,2-Bis(trifluoro-methyl)-4-(3-bromo-2-oxopropyl)-1,3-oxazolidin-5-one was prepared from aspartic acid in a Hantzsch synthesis, using hexafluoroacetone as protecting group.[194]

2-Perfluoroalkylbenzothiazoles **80** ($R_F = C_3F_7$, C_7F_{15}) were prepared by condensation of 2-aminothiophenol with perfluoroacids and cyclization of the corresponding compounds.[196] 2-Trifluoromethylbenzothiazoles have been prepared in a similar way.[182] Thiazoles and benzothiazoles were obtained from the parent heterocycles by reaction with perfluoroalkylperoxides $[X(CF_2)_nO_2CO]_2$ (n = 1-10).[183]



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(iv) Applications

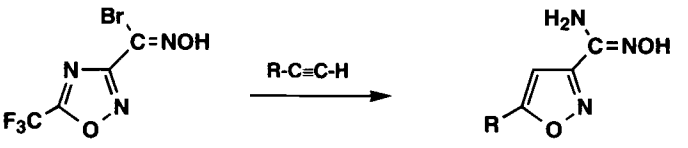
Derivatives **80** are useful as high-temperature lubricants.[196] The properties of thermally stable photochromic *bis*(trifluoromethylthiazolyl)ethenes are expected to be useful in a new series of photodevices.[193] The pharmacological activity of 2-trifluoromethylbenzothiazoles has been reported.[197]

5. Oxadiazoles

1,2,4-Oxadiazoles.

(i) Reactivity

The reaction of 5-trifluoromethyloxadiazole-3-bromoacetyloximes **81** with substituted alkynes or alkenes gave amidoximes **82**.[198]



81 **82**

(ii) Syntheses

Trifluoromethyl-1,2,4-oxadiazoles have been prepared by several groups starting from amidines.[199-201]

1,3,4-Oxadiazoles.

(i) Structure

Trifluoromethyl-1,3,4-oxadiazoles and their cycloaddition products have been studied by MNDO calculations.[144] For references concerning ^{19}F nmr spectroscopy, see § **III.1.**vi.

(ii) Reactivity

Reaction of 3,5-*bis*(trifluoromethyl)-1,3,4-oxadiazoles with primary substituted amines leads to 4-substituted-3,5-*bis*(trifluoromethyl)-1,2,4-triazoles.[127,144] Transformation of oxadiazoles into dihydrotetrazines was achieved by treatment of the former with hydrazine in acidified alcoholic solutions at low temperatures.[202] At p*H* 6 open chained 1-(*N*-aminoperfluoroalkylimidoyl)-2-perfluoroacylhydrazines were obtained as the only product which provided the corresponding 4-amino-1,2,4-triazoles.[135]

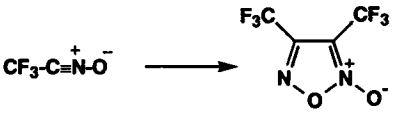
(iii) Syntheses

Condensations of 1,2-*bis*(trifluoroacyl)hydrazines yielding 2,5-*bis*(trifluoro-methyl)-1,3,4-oxadiazole have been described by several groups.[1,138,203-206] Tetrazoles (§ **I.5.**ii) were converted into 1,3,4-oxadiazoles by reaction with perfluoroalkylated acid chlorides followed by pyrolitic elimination of nitrogen.[148] Although less common, trifluoromethyloxazolines have also been reported.[184,207]

1,2,5-Oxadiazoles.

(i) Syntheses

Furoxane **83** was prepared from the corresponding nitrile oxide.[208]



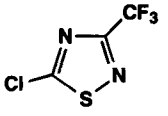
83

6. Thiadiazoles

1,2,4-Thiadiazoles

(i) Syntheses

3-Trifluoromethyl-5-chloro-1,2,4-thiadiazole **84** was prepared by treating the corresponding 3-trichloromethyl derivative with SbF_3/Cl_2 at 150°.[209]



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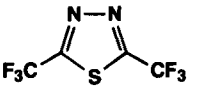

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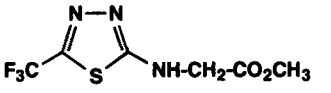


86

1,3,4-Thiadiazoles

(i) Structure

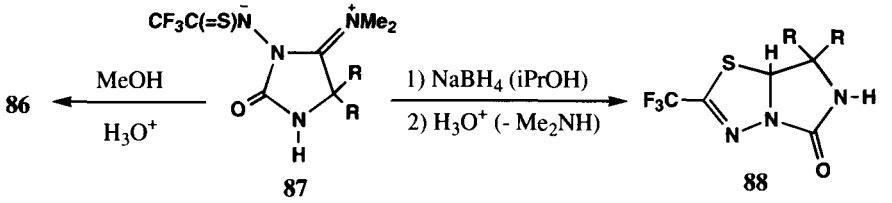
The ^{19}F nmr spectrum of 2,5-*bis*(trifluoromethyl)-1,3,4-thiadiazole **85** has been reported[210] and the ^{19}F and ^{15}N nmr spectra of compound **86** have also been recorded.[211]

(ii) Reactivity

1,3-Dioxolane-2-trifluoromethyl-1,3,4-thiadiazole carbamates were prepared by reacting dioxolanes with appropriate heterocyclic amines.[212]

(iii) Syntheses

The formation of thiadiazoles can be achieved with various procedures.[142,203,204,206] Trifluoromethyldiazomethane reacted with thiazyl chloride (a trimer) to give the thiadiazole **85**.[210] Hydrolysis of the dipolar imidazolone **87** with aqueous hydrochloric acid in methanol surprisingly gave **86**. A mechanism for the reaction has been suggested.[211]



Reduction of **87** with sodium borohydride yielded **88** as the final product. The first step in this reaction is probably the nucleophilic attack of the hydride ion at the amidinium C-atom followed by ring closure with elimination of dimethylamine.[211]

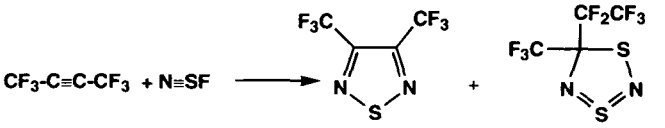
(iv) Applications

The potential of 5-methyl-2-trifluoromethyl-1,3,4-thiadiazole and 2,5-*bis*(trifluoromethyl)-1,3,4-thiadiazole as antiinflammatory, analgesic and antimicrobial agents has been investigated.[197]

1,2,5-Thiadiazoles

(i) Syntheses

The reaction between thiazyl fluoride and hexafluorobutyne yields 3,4-*bis*(trifluoromethyl)-1,2,5-thiadiazole **89** and 5-trifluoromethyl-5-pentafluoroethyl-1,3-dithia-2,4-diazole **90**.[213]

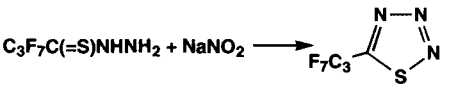


7. Other Heterocycles

1,2,3,4-Thiatriazoles

(i) Syntheses

Brown has described the following reaction which allows one to prepare 5-perfluoropropyl-1,2,3,4-thiatriazole **91**.[142]



III. ^{13}C AND ^{19}F NMR OF PERFLUOROALKYLAZOLES

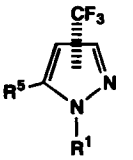
We will discuss in this part some points related to ^{13}C and ^{19}F nmr of trifluoromethyl derivatives of azoles.

1. Fluorine-19 nmr Spectroscopy

For technical reasons, ^{19}F nmr is quite as old as ^{1}H nmr but due to the large scale of fluorine chemical shifts, no compound has appeared to be such a natural reference as TMS has been in proton nmr. Thus, fluorine chemical shifts were (and continue to be) given in literature against a large variety of compounds used as external or internal references, with, in the past, non-uniform sign conventions. In this review, all ^{19}F chemical shifts will be expressed from $CFCl_3$ with positive values for signals at higher frequencies than the reference signal and solvent will be $CDCl_3$ unless stated otherwise. Conversion factors from some references to $CFCl_3$ are according to Wray: TFA : -78.5; C_6F_6 : -162.9; $C_6H_5CF_3$: -63.9; C_6H_5F : -113.15; F_3CCCl_3 : -82.2.[214]

(i) Pyrazoles

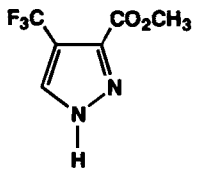
If only one isomer is available with various substituents at other positions, the fluorine chemical shift is not by itself characteristic of the position of the CF_3 group. The situation is different in a homogeneous series. For instance, it has been shown[50] that in compounds **92** (15 compounds in which R^1 and R^5 are aryl substituents), the mean chemical shifts of CF_3 at positions 3 and 4 are -60.0 and -55.3 ppm respectively.



92

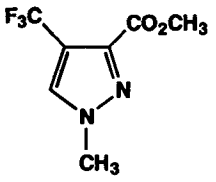
Other examples of 4-CF_3 on substituted pyrazoles are gathered below, showing the dependence of the CF_3 chemical shifts on the substitutents at positions 1, 3 and 5 : **93**, **94**, **95**;[56] **96**, **97**;[58] and **98**.[67]

-58.1



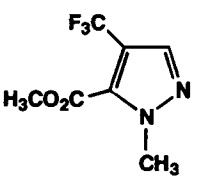
93

-57.1



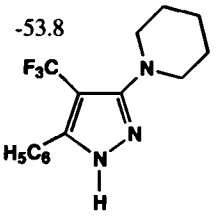
94

-57.8



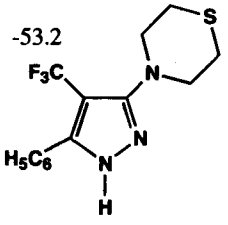
95

-53.8



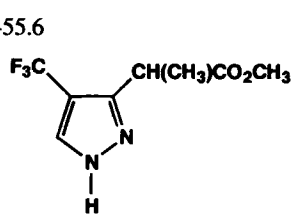
96

-53.2



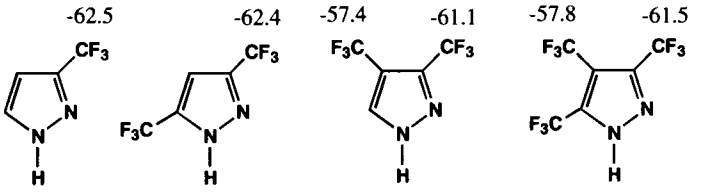
97

-55.6



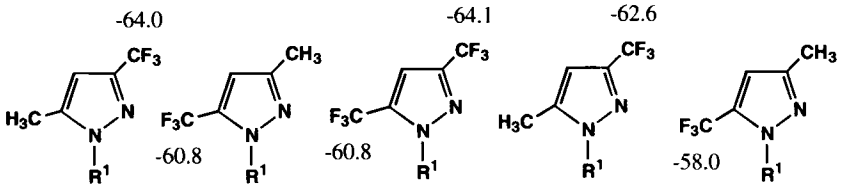
98

In N-H pyrazoles at room temperature, positions 3 and 5 are equivalent due to rapid prototropy (§ **I.1.i**). This is the case for compounds **3**, **6**, **7** and **8**.[13] In compounds **3** and **7**, tautomers **3a** and **3b**, on one hand, and tautomers **7a** and **7b**, on the other, give average signals in ^{19}F nmr spectroscopy.



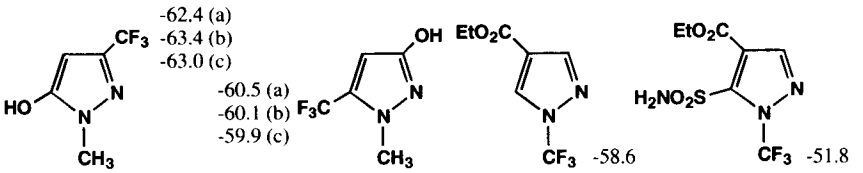
3 **6** **7** **8**

All things being equal, a significant difference is also observed between 3-CF_3 and 5-CF_3 for compounds **99-101** (R^1 = benzothiazol-2-yl)[44] and **102-103** (R^1 = aryl).[33] Metallotropy of *N*-trimethylsilylpyrazoles produces the equivalence of 3- and 5-positions when the temperature is increased.[24] However, in the 1-trimethylsilyl derivative of **6**, the coalescence of the CF_3 signals cannot be obtained [only one CF_3 group is coupled with the protons of the trimethylsilyl substituent, $J(^1H\text{-}^{19}F) = 0.76$ Hz].



99 **100** **101** **102** **103**

The Δ^2-pyrazolin-5-one/Δ^3-pyrazolin-5-one/hydroxypyrazol tautomerism[7] has not been considered by the different authors, when discussing the chemical shifts of 3- and 5-pyrazolinones.[21] The values reported for compounds **104** and **105** in $CDCl_3$ (a),[21] in [$^2H_6$]acetone (b),[49] and in [$^2H_6$]DMSO (c)[19] are given below.



104 **105** **20** **106**

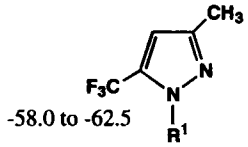
The results concerning **104** and **105** show the low sensitivity of the trifluoromethyl group to solvent effects. However, in the case of 3(5)-trifluoromethyl-5(3)-methylpyrazole **5**, very different chemical shifts have been observed in the same group of solvents:[17] -41.2 in $CDCl_3$, -61.6 in [$^2H_6$]acetone and -51.9 in [$^2H_6$]DMSO. This may be due to a modification in the tautomeric equilibrium constant **5a/5b** (§ **I.1.i**). The ^{19}F chemical shifts of 3-trifluoromethyl-Δ^3-pyrazolin-5-one (-61.4

ppm) and of 3-trifluoro-methyl-4,4-dichloropyrazolin-5-one (a fixed Δ^2-tautomer, -64.0 ppm) have been reported.[16]

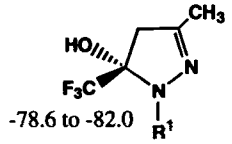
Finally, it appears that 3-CF_3 are generally upfield from 4- or 5-CF_3 in pyrazoles. In the few examples available, the 5-CF_3 appear upfield from the 4-CF_3 signals, but data are missing to draw a general conclusion in the last case. Other data about 3- and(or) 5-CF_3 pyrazoles can be found in refs. 15, 29, 32, 46, 69, 70 and 71; for C_nF_{2n+1} substituted pyrazoles see ref. 21. For a trifluoromethyl group at position 1, *i.e.* linked to the nitrogen, the only available data, compounds **20** and **106**, came from ref. 20.

(ii) Pyrazolines

Some examples of Δ^1-,[13,30,66] Δ^2-,[31-34,58,66] and Δ^3-pyrazolines,[15] substituted by trifluoromethyl groups are described in the literature. The most interesting point is the possibility to differentiate between structures **100** and **107** using the ^{19}F chemical shift of the CF_3 group.[32,33]



100

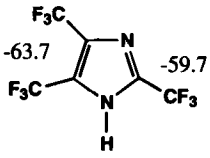


107

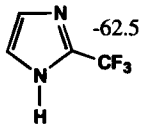
This characteristic 20 ppm upfield shift of a -C(OH)-CF_3 compared to a =C-CF_3 at the 5-position of a pyrazole ring has been pointed out by Singh *et al.*[44] who demonstrated that the 5-CF_3 pyrazoles described in refs. 40 and 41 were in fact the corresponding Δ^2-pyrazolines.

(iii) Imidazoles

Some trifluoromethylimidazoles **108-112** have been studied by ^{19}F nmr (solvent not reported),[93] the most representative being the 2,4,5-trifluoromethylimidazole **108** in which the 4(5)-CF_3 groups appear upfield with regard to the 2-CF_3 group.



108



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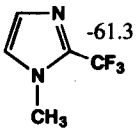

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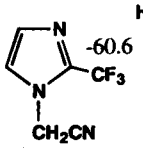
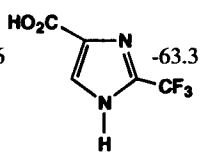


111

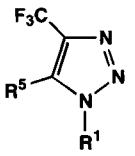


112

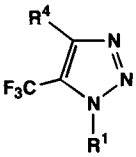
However, the difference between the two positions (4 ppm) is small and the variations of the signal of the 2-trifluoromethyl group, depending on the nature of 1-, 4- or 5-substituents, may be of the same order of magnitude.

(iv) Triazoles

Ten 1-substituted-1,2,3-triazoles of the types **113** and **114** have been investigated by ^{19}F nmr,[133] and the conclusion of the authors is that the trifluoromethyl group at the 4-position of the 1,2,3-triazole ring resonates at higher field than that at the 5-position (mean values -59.9 and -56.6 respectively).

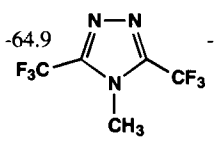


113

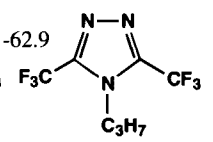


114

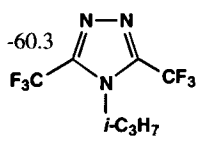
A series of 4-substituted 3,5-*bis*(trifluoromethyl)-1,2,4-triazoles **115-118** have been studied by Reitz and Finkes.[135,136] Their chemical shifts are very similar to those found in other azoles.



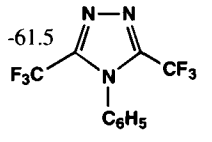
115



116



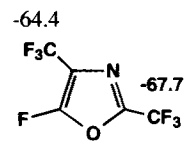
117



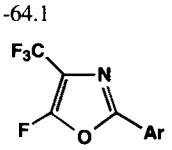
118

(v) Isoxazoles, oxazoles, isothiazoles and thiazoles

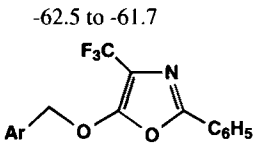
From data on compounds **71** (R = CF_3)[207] and **71** (R = Ar),[179] it appears that 2-CF_3 is upfield from 4-CF_3, but not enough data are available to generalize this observation. Different compounds **119** and **120**, which differ in the nature of Ar, are reported below;[167] the range of values is indicated and it may be observed that, as in the pyrazole/pyrazoline case, the chemical shift of the CF_3 group is characteristic of the isomer which is obtained. The few data available on isoxazoles come from refs. 69 and 153.



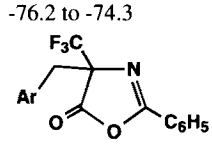
71, R = CF_3



71, R = Ar

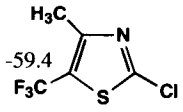


119

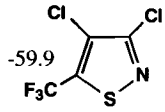


120

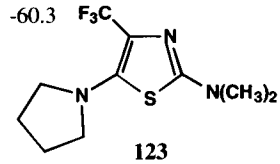
For thiazoles and isothiazoles in $CDCl_3$ **121-126**,[57,165] 4-CF_3 or 5-CF_3 groups are downfield with regard to those at 2- or 3-positions :



121



122



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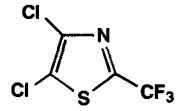
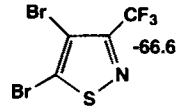


124



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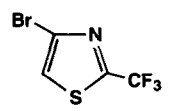
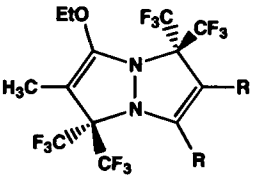


126

(vi) Other Heterocycles

Fluorine data can be found for CF_3 groups on some miscellaneous heterocycles and their derivatives and among them 1,3,4-oxadiazoles,[126,135] 1,3,4-thiadiazoles,[210] oxazolidin-5-ones,[176,177,185] 1,5-diazabicyclo[3.3.0]octa-2,6-diene **127**,[14] and 2,3,4-triazabicyclo-[3.2.0]hepta-2,6-diene **48**.[131]



127

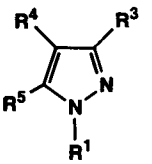
2. Carbon-13 nmr Spectroscopy

This study will be mainly concerned with the chemical shifts (in ppm/TMS) of the CF_3 group itself and to a lesser extent with the carbon atom bearing it since the effects of the other substituents cannot be left out. In the pyrazole series, substituent effects have already been reported.[215] We will be also interested in the C-F coupling constants which are indicated between parentheses in the corresponding tables.

(i) Pyrazoles

As observed in the selected examples of Table 2, neither the chemical shift of the CF_3 group (about 122 ± 2 ppm) nor the $^1J_{CF}$ (267 ± 1 Hz) can be considered as characteristic of the position of the substituent on the pyrazole ring.

TABLE 2. ^{13}C Chemical Shifts (δ) and ^{13}C-^{19}F Coupling Constants (Hz,in parentheses) of Selected CF_3-substituted Pyrazoles in $CDCl_3$



No	R^1	R^3	R^4	R^5	C_3	C_4	C_5	CF_3	Ref.
93	H	CO_2Me	CF_3	H	139.6	114.2 (43.5)	132.4	121.8 (266.4)	[56]
94	CH_3	CO_2Me	CF_3	H	138.6	113.8 (39.3)	131.5 (4.6)	120.5 (266.9)	[56]
95	CH_3	H	CF_3	CO_2Me	135.65 (4.0)	114.8 (38.7)	129.4 (2.4)	120.5 (266.9)	[56]
99	BzTh[a]	CF_3	H	CH_3	144.7 (38.9)	—	—	120.7 (269.2)	[44]
100	BzTh[a]	CH_3	H	CF_3	—	—	133.0 (41.2)	119.3 (268.5)	[44]
101	BzTh[a]	CF_3	H	CF_3	144.3 (41.2)	—	134.3 (42.7)	119.7 (270.2), 118.6 (270.1)	[44]
102	H	CF_3	H	CH_3	142.9 (37)	102.9	141.6	121.6 (268)	[17]
103[b]	H	CF_3	H	CF_3	138.2 (38.6)	104.7 (1.7)	138.2 (38.6)	120.6 (267.9)	[22]
104[b]	CH_3	CF_3	H	OH	139.0 (37.1)	84.8 (2.2)	153.5	122.0 (268.1)	[19]
105[b]	CH_3	OH	H	CF_3	160.3	92.8 (2.6)	131.2 (38.2)	120.2 (268.0)	[19]

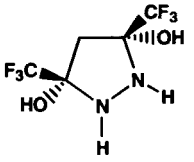
a) BzTh = benzothiazo l-2-yl. b) In [$^2H_6$]DMSO.

In the case of hydroxypyrazoles **104** and **105** (§ **III.1**.i), ^{13}C nmr spectroscopy proved useful to determine both isomerism and tautomerism (no CH-tautomer was found for **104**).[49] In compound

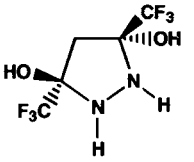
105 there is a $^4J_{CF}$ = 1.0 Hz between the *N*-methyl group and the 5-CF_3 substituent. Other data on pyrazoles can be found in references 21, 42, 46, 49, 63, 67 and 69.

(ii) Δ^2-Pyrazolines and pyrazolidines

Data on compounds **128-131** are reported on Table 3.



128



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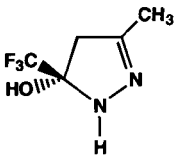

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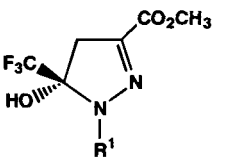

131

TABLE 3. ^{13}C Chemical Shifts (δ) and ^{13}C-^{19}F Coupling Constants (Hz, in parentheses) of Pyrazolidines and Δ^2-pyrazolines

No	Solvent	C_3	C_4	C_5	CF_3	Ref.
128	[$^2H_6$]DMSO	92.4 (30.1)	45.6	92.4 (30.1)	124.9 (285.9)	[31]
129	[$^2H_6$]DMSO	92.6 (29.8)	45.1	92.6 (29.8)	124.4 (285.2)	[31]
130	[$^2H_6$]DMSO	148.4	45.1	91.1 (30.1)	124.4 (282.3)	[31]
131 (R^1 =H)	[$^2H_6$]acetone	—	—	93.0 (31.7)	124.5 (281.6)	[34]
131 ($R^1 = C_6H_5$)	$CDCl_3$	—	—	94.8 (32.9)	122.9 (285.3)	[34]

(iii) Imidazoles

Data on some representative trifluoromethylimidazoles from ref. 116 are reported in Table 4.

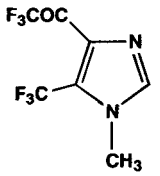

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TABLE 4. ^{113}C Chemical Shifts (δ) and ^{13}C-^{19}F Coupling Constants (Hz, in parentheses) of Selected CF_3-substituted Imidazoles in $CDCl_3$

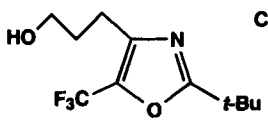
No	R^1	R^2	R^4	R^5	C_4	C_5	CF_3	Ref.
42	CH_3	H	CF_3	$C_6H_4CH_3$	128.8 (37.4)	114.8 (38.5)	122.5	[116]
43	CH_3	H	$C_6H_4CH_3$	CF_3	145.1	116.5 (39.1)	121.7	[116]
132	CH_3	H	$COCF_3$	CF_3	135.5 (4.9)	127.2 (35.4)	119.8	[116]
133	$C(CH_3)_3$	H	*i*-C_3H_7	CF_3	153.6 (2.9)	114.8 (38.5)	122.5	[116]

(iv) Other Heterocycles

Most data concern isothiazoles, **122**, **125** and thiazoles **124**, **126** (Table 5), oxazoles and their derivatives, **119**, **120**, **134-137**, **78**, **79** (Table 6). Partial results can also be found for 4*H*-1,2,4-triazole derivatives,[135,137] for thiazoles,[57] for isoxazoles[69] and for oxazolidinones.[185]

TABLE 5. ^{13}C Chemical Shifts (δ) and ^{13}C-^{19}F Coupling Constants (Hz, in parentheses) of Selected CF_3-substituted Isothiazoles and Thiazoles in $CDCl_3$

No	C_2	C_3	C_4	C_5	CF_3	Ref.
122	—	150.3	123.7 (2.9)	149.3 (39.0)	119.9 (270.0)	[165]
125	—	155.1 (39.5)	111.4	139.5	118.4 (274.5)	[165]
124	151.3 (46.0)	—	138.9	125.1 (2.5)	118.1 (273)	[165]
126	155.9	—	126.6	120.5	118.5 (269)	[165]



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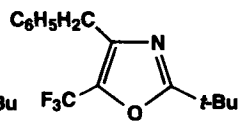
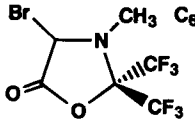
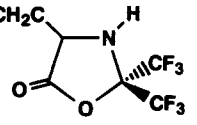


135



136



137

TABLE 6. ^{13}C Chemical Shifts (δ) and ^{13}C-^{19}F Coupling Constants (Hz, in parentheses) of Selected CF_3-substituted Oxazoles, Oxazolidinones and Oxazolines in $CDCl_3$

No	C_2	C_4	C_5	CF_3	Ref.
119[a]	152.7-153.1	108.2-108.7 (40-41)	151.1-155.8 (3)	118.1-121.2 (266-267)	[167]
120[a]	163.8-164.8	75.7-78.2 (24-28)	171.0-171.4 (1-2)	122.3-122.6 (284-285)	[167]
134	172.19	141.57 (2.5)	133.85 (42.4)	119.81 (267.2)	[167]
135	162.18	142.30 (2.0)	134.15 (42.0)	119.93 (267.9)	[167]
136[b]	89.5 (34)	63.9	163.1	119.9 (289),120.2 (292)	[167]
137	88.4 (35)	50.9	171.0	120.2 (285), 121.4 (289)	[167]
78	—	—	—	123.7 (280.8)[c], 124.6 (279.5)[d]	[184]
79	—	—	—	123.7 (282.8),[c] 123.6 (281.1)[d]	[184]

a) Depending on the nature of R (§ **III.1.**v). b) *N*-methyl at 32.1 ppm; [c] *cis*; [d] *trans*;

In the case of compounds **78** and **79** (§ **II.3.**iii), the coupling constants $^3J_{CF}$ of C_5 are between 2.3 and 2.7 Hz for *trans* isomers and zero for *cis* isomers. Moreover, the chemical shift of the CF_3 groups are insensitive to the *cis-trans* isomerism but those of the quarternary carbons of 5-phenyl groups are dependent on the stereochemistry.

As a first conclusion concerning this nmr survey on trifluoromethylazoles, it appears that the carbon chemical shifts of the CF_3 groups (about 120 to 124 ppm) is characteristic neither of the azole to which it is attached nor of the position of the substitution on the azole ring. The $^1J(^{13}C$-$^{19}F)$ coupling constant is only affected by the hybridization of the carbon bearing the CF_3 group (265 to 275 Hz for sp^2 and 280-290 Hz for sp^3 carbons). Fluorine chemical shifts are slightly more sensitive

than carbon ones and, for instance, in a series of related compounds it allows one to determine the position of the CF_3 group on a pyrazole ring. In contrast to what has been observed in ^{13}C nmr, CF_3 fluorine signals are significantly shifted upfield when the carbon bearing the CF_3 group is an sp^3 carbon atom.

IV. CONCLUSION

This survey of trifluoromethylazoles reveals that the biological properties and the synthetic aspects have been covered comprehensively. The reactivity studies, in particular the reactions involving the CF_3 group, are scarce but they are not very interesting. Finally, both the structural studies and the study of physical properties deserves to be explored with much more attention.

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