5-Halomethyl-5-Hydroxy-4,5-Dihydroisoxazoles: Synthesis and ^{13}C, ^{17}O, ^{15}N, ^{19}F NMR Spectroscopy

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Abstract: This review reports the synthesis and isolation of close to 125 5-haloalkyl substituted 5-hydroxy-4,5-dihydroisoxazoles. The 4,5-dihydroisoxazoles were mainly obtained from the reaction of β-diketones or β-alkoxyvinyl ketones with hydroxylamine, using different reaction conditions and methodologies. The review also reports the ^{13}C NMR data for 109 compounds, the ^{17}O NMR data for 17 compounds, the ^{15}N NMR data for 16 compounds and the ^{19}F NMR data for 36 compounds. The empirical additive substituent increments (SCS) were determined from the experimental ^{13}C, ^{17}O and ^{15}N NMR data.

Keywords: Isoxazoles, 4,5-dihydroisoxazoles, ^{13}C, ^{17}O, ^{15}N and ^{19}F NMR, heterocyles, halomethylated compounds.

1. INTRODUCTION

Heterocyclic compounds are very widely distributed in nature and are essential to life. There are a vast number of pharmacologically active heterocyclic compounds, many of which are of regular clinical use. Among these compounds, azoles are heterocycles with extensive biological properties [1,2]. Their importance as active drugs for medical applications is demonstrated by the fact that they represent, on average, 3% of the compounds in the MDL Drug Report (MDDR-3D) and 1.6% of the entries in the Comprehensive Medicinal Chemistry (CMC-3D) annually [3]. The search for new azole structures is a matter of great relevance, as a comprehensive library of these compounds is very much desired for biological studies and as there is considerable interest in their herbicidal, fungicidal, insecticidal, analgesic, antipyretic and anti-inflammatory properties [4-6]. Azoles constituted of a five membered ring system containing one oxygen and one nitrogen atom adjacently are known as isoxazoles. Among these, there are the non-aromatic heterocycles: 4,5-dihydroisoxazoles (**I**), 2,3-dihydroisoxazoles (**II**) and 2,5-dihydroisoxazoles (**III**) and the aromatic heterocycles, isoxazoles (**IV**) Fig. (**1**). The 4,5-dihydroisoxazoles (**I**) have also been previously known as Δ^2-isoxazoles or 2-isoxazolines.

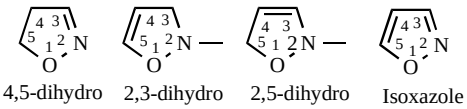

Fig. (1). Isoxazoles.

Isoxazoles and their non-aromatic derivatives are highly useful in several fields, and in particular, in the fields of agriculture and medicine [7-9]. Most recently, these compounds have been found to be integral part of the selective inhibitors of human transglutaminase 2, thus demonstrating their importance as prototypes for the treatment of Huntington's, Alzheimer's and Parkinson's diseases [10]. Other pharmacological activities of this core include the potent and selective antagonism of the NMDA receptor [11], antagonism of the $GABA_A$ receptor, in the low nanomolar range, [12] and *in vitro* antiprotozoal activities [13].

Among the dihydroisoxazoles, 4,5-dihydroisoxazoles (Fig. (**1**)) have been found to be the most important non-aromatic isoxazoles because these compounds are mainly used as synthetic intermediates and as a structural model for spectroscopic studies [7].

In recent years, the importance of haloalkyl-substituted heterocyclic compounds has been evidenced by many authors [14-16]. This is easy to understand when considering a 5-haloalkyl group, e.g., the trifluoromethyl group. The presence of this substituent in heterocyclic compounds, especially at a strategic position of drug molecules, has become an important facet of pharmaceutical research because of the unique physical and biological properties of fluorine [14]. The steric requirement of the fluorine atom resembles that of hydrogen (van der Waals radii: CF_3 = 1.35 Å *versus* CH_3 = 1.29 Å). Thus, substitution of a methyl by a trifluoromethyl group in a drug candidate usually allows the trifluoromethylated analog to be of comparable size and follow similar drug-protein interactions as those of the parent methyl compound. However, the strong covalent bonding of the C–F bond (116 kcal·mol^{-1}), in contrast to that of the C–H bond (100 kcal·mol^{-1}) [15] is often capable of avoiding unwanted metabolic transformations [16]. Therefore, such alterations can be used constructively by medicinal chemists to improve both the safety and the efficacy of a drug. The high electronegativity of fluorine enables a trifluoromethyl group to decrease the electron density and basicity or to enhance the electrophilicity of the neighboring functional groups within a molecule. In many systems, the substitution of a methyl group by a trifluoromethyl group results in added lipophilicity ($\pi_{(CF3)}$ = 1.07 versus $\pi_{(CH3)}$ = 0.50) [17] which may lead to easier absorption and transportation of the molecules within biological systems and thereby improve the overall pharmacokinetic properties of drug candidates. On

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the other hand, the importance of chlorinated compounds has also been observed in synthetic synthoms, e.g., the versatility of the trichloromethyl group in organic synthesis as a leaving group or as a precursor of carboxylic acids, esters and carboxamide groups [18].

A great deal of attention has been given to 5-hydroxy-4,5-dihydroisoxazoles as these compounds are not normally isolated because they are labile compounds and readily dehydrate to aromatic isoxazole [7]. However, when there is a strong withdrawing group attached at the 5-position of the ring, the 5-hydroxy-4,5-dihydroisoxazoles becomes very stable and isolable. The main withdrawing groups reported to stabilize these compounds are the 5-haloalkyl groups [18]. 5-trifluoro[chloro]methyl-5-hydroxy-4,5-dihydroisoxazoles are stable compounds and for their conversion to aromatic isoxazoles, it is necessary to stir them in concentrated sulfuric acid for a few hours [19,20]. It is believed that the dehydration reaction of 4,5-dihydroisoxazoles in acid media (HA) is a second order elimination reaction E2 (*E1-like transition state*), where the stability of the activated complex depends on the participation of the electron pair of the neighboring oxygen atom (O-1) present in the isoxazole ring and on the electron donation effect of the R^3 group attached on the C-5 of the isoxazole ring, (Fig. (**2**)).

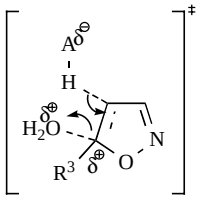
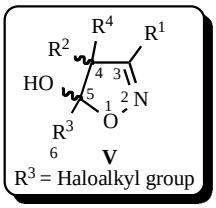


Fig. (2). Probable structure of the activated complex in the E2 (*E1-like transition state*) dehydration reaction of a 4,5-dihydroisoxazole.

In the literature, there are some reviews describing organic fluorinated compounds in heterocyclic chemistry, e.g., the synthesis of α,β-unsaturated ketones bearing a trifluoromethyl group and their application in organic synthesis [21,22]; the structure, synthesis and reactivity of trifluoromethyl- and perfluoroalkyl-derivatives of azoles [23]; the synthesis of trifluoromethyl-substituted saturated cycles [14]; and the NMR spectroscopy of isoxazoles [24]. On the other hand, there is only one review in the literature describing organic chlorinated compounds in heterocyclic chemistry [18].

Thus, considering the importance of 4,5-dihydroisoxazoles (**I**) and the lack of reviews on these compounds, the aim of this review is to examine the synthesis of 5-hydroxy-4,5-dihydroisoxazoles-5-haloalkyl substituted (**V**). The ^{13}C, ^{17}O, ^{15}N and ^{19}F NMR data of these compounds will also be presented.



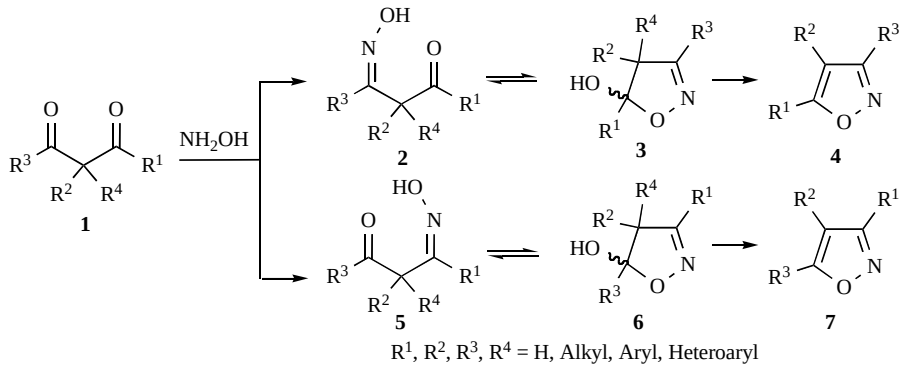
V

2. SYNTHESIS

The synthesis of isoxazoles has been relatively well explored using the so-called [*3+2*] atom fragment, where the number represents each synthom component, which is then subdivided by the type and arrangement of ring atoms in each component. For example, [CCC+NO] represents the reaction between diketone or α,β-unsaturated ketone and hydroxylamine. [CNO+CC] represents nitrile N-oxide and alkenes or alkynes [7]. However, with non-symmetrical starting materials (CCC or CC), neither of these methods is completely unequivocal in regard to controlling the regiochemistry of the reaction, which depends on the structural effects of the starting materials, the stability of the ring formed and/or on reaction conditions [7,18]. The main route for the synthesis of 5-hydroxy-4,5-dihydroisoxazoles is the [CCC+NO] route, from the cyclocondensation of β-diketones or β-alkoxyvinyl ketones with hydroxylamine [6,11].

Reports in the literature [7] indicate that the 5-hydroxy-4,5-dihydroisoxazole system exists in solution as equilibrium between the ring (**3** and **6**) and open-chain forms (**2** and **5**). The direction of the equilibrium depends on the structural effects of the starting materials, the stability of the ring formed and/or on reaction conditions [7,18], e.g., by increasing the bulk and/or number of substituents favouring the cyclic form. In the cyclic form, the hydroxyl substituent is relatively labile and dehydration to the respective isoxazoles (**4** and **7**) occurs readily [7], (Scheme **1**).

Some reports have discussed the influence of the variation of pH on the equilibrium between the free hydroxylamine and its protonated and deprotonated forms. It seems obvious that the more nucleophilic end of hydroxylamine will be the nitrogen atom, however, that depends on the pH



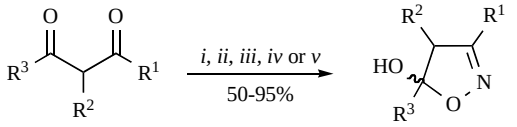
Scheme 1.

of the solution. Bases such as pyridine or sodium acetate produce some of the reactive neutral hydroxylamine in the presence of the less reactive cation, but bases such as sodium ethoxyde produce the anion. Usually the reactions are carried out in pyridine [7]. Nevertheless, the influence of the variation of pH was not an important factor in the regiochemistry of the closure of the isoxazole ring when these compounds were obtained from the cyclocondensation of β-alkoxyvinyl halomethyl ketones or β-halomethyldiketones with hydroxylamine [18].

2.1. Preparation of 4,5-Dihydroisoxazoles from β-Diketones

The simplest way to obtain the haloalkyl substituent in heterocycles is by introducing a haloalkyl group in the heterocyclic precursor before cyclization. Diketones and α,β-unsaturated ketones are the most common precursors used. These precursors have two electrophilic sites, which enables two places for the nucleophilic attack from hydroxylamine. The presence of a haloalkyl group in these precursors is important for the regiochemistry of the ring closure due its great electronic effects, which change the electron-density distribution and, consequently, the relative reactivity of the carbonyl groups. The haloalkyl group is also responsible for stabilizing the hemi-acetal formed with the 4,5-dihydroisoxazole ring [18].

In 1974, Escale *et al.* [25] reported the first 5-haloalkyl-5-hydroxy-4,5-dihydroisoxazole **9** (Entry 1) in the literature. To avoid dehydration to isoxazole, the compound was prepared in pyridine at a low temperature, (Scheme **2**). The next



8 **9**

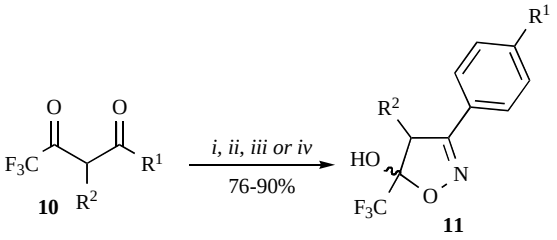
i: NH_2OH, $CHCl_3$, Pyridine, 0-15°C (Yield: 50%)
ii: NH_2OH●HCl, MeOH, 40°C, 5-8 h (Yield > 90%)
iii: NH_2OH, EtOH, NaOH, 45 min (Yield: 91%)
iv: NH_2OH●HCl, (Yield: higher than 95%)
v: 2 NH_2OH●HCl, HCl, 12 h (Yields: 83-94%)

Entry	Method	R^3	R^2	R^1	Ref.
1	*i*	CH_2Cl	H	Me	[25]
2	*ii*	CCl_3	H	Me	[29]
3	*ii*	CCl_3	H	Ph	[29]
4	*ii*	CCl_3	Me	Ph	[29]
5	*ii*	CCl_3	Et	Ph	[29]
6	*ii*	CCl_3	-$(CH_2)_4$-		[29]
7	*ii*	CCl_3	-[$(CH_2)_2$(CH-*tert*-Bu)CH_2]-		[29]
8	*ii*	CCl_3	-$(CH_2)_5$-		[29]
9	*ii*	CCl_3	-$(CH_2)_6$-		[29]
10	*iii*	CF_3	H	Ph	[27]
11	*iv*	CF_3	H	(Cl-4-F-2-OMe-5)-Ph	[28]
12	*iv*	CF_3	H	(Cl-4-F-2-Me-5)-Ph	[28]
13	*iv*	CF_3	Cl	(Cl-4-F-2-OMe-5)-Ph	[28]
14	*iv*	CF_3	Cl	(Cl-4-F-2-Me-5)-Ph	[28]
15	*v*	$(CF_2)_2CF_3$	H	Ph	[26]
16	*v*	$(CF_2)_4CF_3$	H	Ph	[26]
17	*v*	$(CF_2)_6CF_3$	H	Ph	[26]
18	*v*	$(CF_2)_6CF_3$	H	*tert*-Bu	[26]
19	*v*	$(CF_2)_6CF_3$	H	$(CF_2)_6CF_3$	[26]

Scheme 2.

year, Massyn *et al*. [26] had already synthesized polifluoro alkyl compounds (Entries 15-19) using one equivalent of β-diketone **8** and two equivalents of hydroxylamine in hydrochloride acid, (Scheme **2**). Félix *et al.* [27] prepared the 5-trifluoromethyl-5-hydroxy-4,5-dihydroisoxazole (Entry 10) for the addition of hydroxylamine to β-diketone **8** at a molar ratio of 1:1 using ethanol as solvent. In 2004, Zhou *et al*. [28] reported the syntheses of the four dihydroisoxazoles (Entries 11-14) with the attainment of different substituted groups through the following steps. Substituted acetophenone was treated with ethyltrifluoroacetate in the presence of sodium methoxide to obtain substituted phenyl-4,4,4-trifluoro-1,3-butanedione, which was chlorinated in methylene dichloride at room temperature. Finally, phenyl-4,4,4-trifluoro-1,3-butanediones were reacted with hydroxylamine hydrochloride to give the corresponding dihydroisoxazole ring. The total yields of the titled products were higher than 95%. In 2005, Martins *et al*. [29] reported an improved method for the synthesis of a new series of trichloromethyl-β-diketones **8** (Entries 2-9) as well as their use in cyclocondensation reactions with hydroxylamine hydrochloride leading to the respective 4,5-dihydroisoxazoles **9** (Entries 2-9), (Scheme **2**).

Recently, Kumar *et al*. [30] showed the reaction of hydroxylamine hydrochloride with aryl trifluoromethyl-β-diketones **10** performed at different pH levels, (Scheme **3**). The reaction conditions involved the reactants in the presence of sulfuric acid (pH = 0.3), sodium acetate (1 and 2 mol equiv, pH = 6.7 and 8.1, respectively) and sodium bicarbonate (pH = 6.9) using ethanol under reflux as solvent. Regardless of the pH of the medium, the products were identified as 3-aryl-5-hydroxy-5-trifluorormethyl-4,5-dihydroisoxazoles **11**. Thus, we observed that the pH did not modify the regiochemistry of the reaction. In the same paper, the authors reported the reaction of 1-aryl-2-(4-fluorophenyldiazo)-4,4,4-trifluorobutane-1,3-diones **10** with hydroxylamine hydrochloride carried out in the presence of sodium acetate (1 mol equiv) under reflux of ethanol for 4 hours to furnish the 5-trifluorormethyl-4,5-dihydroisoxazole derivatives **11**, (Scheme **3**).

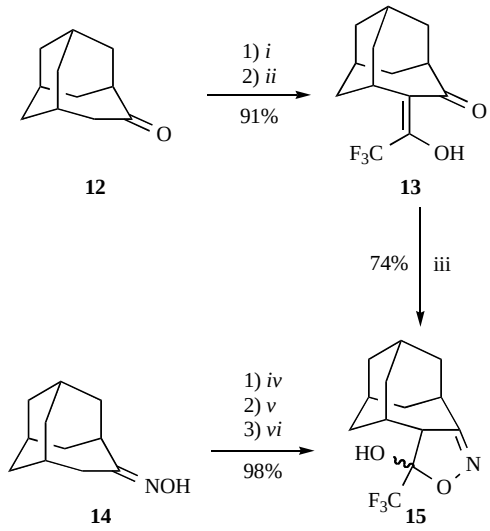


i: $NH_2OH{\bullet}HCl$, EtOH, reflux, 4 h
ii: $NH_2OH{\bullet}HCl$, H_2SO_4, EtOH, reflux, 4 h
iii: $NH_2OH{\bullet}HCl$, AcONa 1 Eq., EtOH, reflux, 4 h
iv: $NH_2OH{\bullet}HCl$, AcONa 2 Eq., EtOH, reflux, 4 h
v: $NH_2OH{\bullet}HCl$, $NaHCO_3$, EtOH, reflux, 4 h

R^1 = H, OMe, F, Cl, Br, NO_2
R^2 = H Method: *i, ii, iii or iv* (Ref. [30])
R^2 = N=N(F-4-Ph) Method: *iii* (Ref. [30])

Scheme 3.

Trifluoroacetylation of 4-homoadamantanone **12** with sodium hydride, followed by ethyl trifluoroacetate at 90°C in a sealed tube afforded a 5-trifluoroacetyl derivative **13** in good yield (91%), (Scheme **4**). The regiospecific synthesis of 4,5-dihydroisoxazole **15** from trifluoracetylated 4-homoadamantanone **13** was carried out in pyridine under reflux of ethanol, (Scheme **4**). The regiochemistry was confirmed by an alternative synthesis from the known oxime **14**. Under appropriate conditions, the inversion of the regiochemistry occurred without isolation of the intermediate 2,3-dihydroisoxazoles leading to 3-trifluoromethylisoxazole [31].



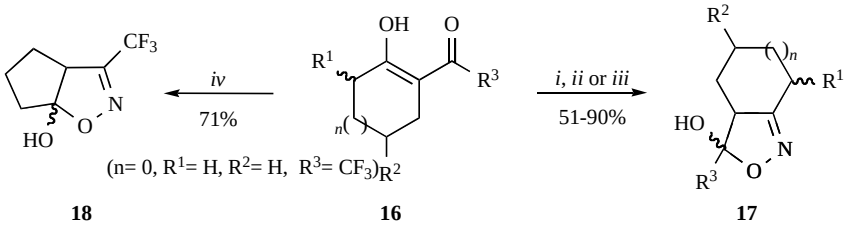
i: NaH, THF, 90°C, 1 h
ii: CF_3CO_2Et, 90°C, 3 h
iii: $NH_2OH{\bullet}HCl$, Pyridine, EtOH, 78°C, 3 h
iv: BuLi, THF , 0°C, 1 h
v: CF_3CO_2Et , 0°C, 0.5 h
vi: 2*N* HCl, reflux, 2 h

Scheme 4.

The reactions of haloacetylcycloalkanones **16** with hydroxylamine have, in most cases, led to the formation of regiospecifically fused 5-haloalkyl-4,5-dihydroisoxazoles **17**, where the amino group added on the carbonyl group of the cycloalkanone ring followed by cyclization led to the formation of a stable hemi-acetal [32-34], (Scheme **5**). In these reactions, it has been shown that the pH did not influence the regiochemistry of the cyclization. The use of aqueous pyridine or aqueous hydrochloric acid led to the same 5-haloalkylisoxazole derivatives **17** (Entries 3 and 4) [32a]. The structure of compound **17** (Entry 4) was studied from the ^1H and ^{13}C data, AM1 calculations and X-ray diffraction [32b]. ^1H and ^{13}C data shown that only one pair of the diasteriosiomers was obtained, and the AM1 calculations indicated that the (3S3aS/3R3aR)-diastereoisomer pair is 2.63 $kcal.mol^{-1}$ more stable than the (3S3aR/3R3aS)-diatereoisomer pair. The X-ray diffraction data confirmed that only the structure (3S3aS/3R3aR)-diastereoisomer pair was obtained. The configuration of (3S3aS/3R3aR)-dia-stereoisomer pair has the less strained condensed ring system, where the bulky CCl_3 group is cis to H3a and OH group is cis to the C-C bond of cyclohexane ring [32b].

The reaction of 2-trifluoroacetyl cyclopentanone or its β-methoxyvinyl trifluoromethyl ketone derivative with hydroxylamine hydrochloride presented an unusual behavior. These reactions were carried out in a hydrochloric acid me-

dium and furnished the 3-trifluoromethyl-4,5-trimethylene-5-hydroxy-4,5-dihydroisoxazole **18** in 71 % yield [35] (Scheme **5**). This inversion of the regiochemistry with the oxygen atom directly attached to the carbocycle carbon was attributed to the thermodynamically unfavorable formation of C=N at the junction of two condensed five-membered rings. On the other hand, 2-polyfluoroacetylcyclohexanones **16** (Entries 1 and 2, 12-15) reacted with hydroxylamine to afford exclusively the 5-polyfluoroalkyl-5-hydroxy-4,5-dihydroisoxazole derivatives **17** (Entries 1 and 2, 12-15) [33] (Scheme **5**). Recently, Flores *et al*. [34] reported the cyclocondensation reaction of ω-bromo-α-trifluoroacetylcycloalkanones **16** (Entries 9-11) and others α-trifluoroacetylcycloalkanones (Entries 6-8) with hydroxylamine hydrochloride, (Scheme **5**). The reaction regiospecifically furnished 5-trifluoromethyl-5-hydroxy-4,5-dihydroisoxazole derivatives **17** (Entries 6-11) regardless of the ring size or ω-substituent.

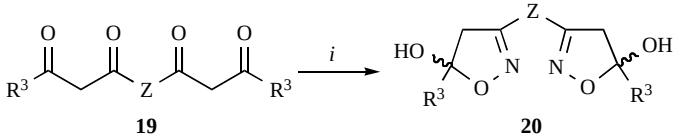


18 **16** **17**

i: $NH_2OH\bullet HCl$, H_2O, Pyridine or HCl, 45-50°C, 8 h
ii: $NH_2OH\bullet HCl$, Et_3N, PrOH, $BF_3\bullet OEt_2$, reflux, 2-15 h
iii: $NH_2OH\bullet HCl$, MeOH, 50°C, 8 h
iv: $NH_2OH\bullet HCl$, H_2O, HCl 12 *N*, 50°C, 12 h

Entry	Method	*n*	R^1	R^2	R^3	Ref.
1	*ii*	0	H	H	CF_2CF_2H	[33]
2	*ii*	0	H	H	$(CF_2)_3CF_3$	[33]
3	*i*	1	H	H	$CHCl_2$	[32]
4	*i*	1	H	H	CCl_3	[32]
5	*i*,*ii*	1	H	H	CF_3	[32,33]
6	*iii*	1	H	*tert*-Bu	CF_3	[34]
7	*iii*	2	H	H	CF_3	[34]
8	*iii*	3	H	H	CF_3	[34]
9	*iii*	1	Br	*tert*-Bu	CF_3	[34]
10	*iii*	2	Br	H	CF_3	[34]
11	*iii*	3	Br	H	CF_3	[34]
12	*ii*	1	H	H	CF_2CF_2H	[33]
13	*ii*	1	H	H	$(CF_2)_2CF_3$	[33]
14	*ii*	1	H	H	$(CF_2)_3CF_2H$	[33]
15	*ii*	1	H	H	$(CF_2)_5CF_3$	[33]

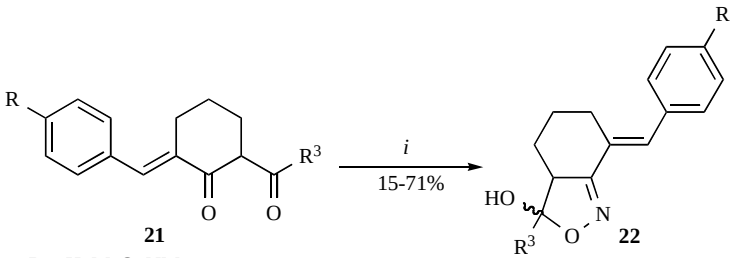
Scheme 5.



19 **20**

R^3 = CF_3, $CF_2CF_2CF_3$, $CF_2CF_2CF_2CF_3$
Z = $-(CH_2)_2-$, -1-Ph-4-
i: 2 $NH_2OH\bullet HCl$

Scheme 6.

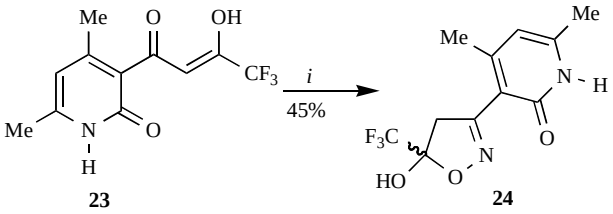


Scheme 7.

In 1999, Chizhov *et al*. [36] reported the synthesis of polyfluoroalkyl-*bis*-5-hydroxy-4,5-dihydroisoxazoles **20** from the reaction of polyfluoroalkyl-*bis*-β-diketones **19** with hydroxylamine hydrochloride, (Scheme **6**).

The polyfluoroalkyl-(*E*)-4-alken-1,3-diones **21** reacted with hydroxylamine hydrochloride in the presence of BF_3•OEt_2, furnishing the corresponding 5-polyfluoroalkyl-5-hydroxy-4,5-dihydroisoxazoles **22**, (Scheme **7**). In this case, the product yields depended on the length of the (polyfluoroalkyl)substituent in the substrate molecule. For $R^3 = CF_3$, the yields were 58% (R^1 = H) and 71% (R^1 = MeO), while for $R^3 = C_4F_9$, R^1= NMe_2, the yield was only 15% [33].

In 2003, Sosnovskikh *et al*. [37] studied the reactions of 5,7-dimethyl-2-trifluoromethyl-8-azachromone **23** with several *N*-nucleophiles. The reaction with hydroxylamine hydrochloride in the presence of sodium acetate and under reflux of ethanol for 1h affording the 3-[5-hydroxy-5-trifluoromethyl-4,5-dihydroisoxazol-3-yl]-4,6-dimethylpyridin-2(1*H*)-one **24** in 45% yield [37], (Scheme **8**).

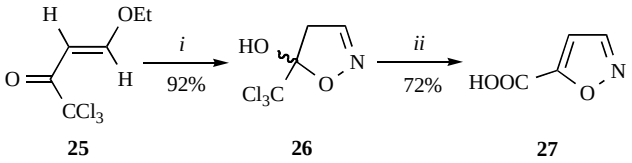


Scheme 8.

2.2. Preparation of 4,5-Dihydroisoxazoles from β-Alkoxyvinyl Ketones

BASF (Germany) patents showed the first synthesis of 5-trichloromethyl-5-hydroxy-4,5-dihydroisoxazoles from the reaction of β-alkoxy halomethyl ketones with hydroxylamine hydrochloride, and their application as intermediates in the preparation of agrochemical and pharmaceutical compounds [38-41]. Isoxazole-5-carboxylic acid **27** was obtained from the dehydration of 5-hydroxy-5-trichlorometyl-4,5-dihydroisoxazole **26** with the subsequent hydrolysis of the trichloromethyl group by treatment with concentrated sulfuric acid [19], (Scheme **9**).

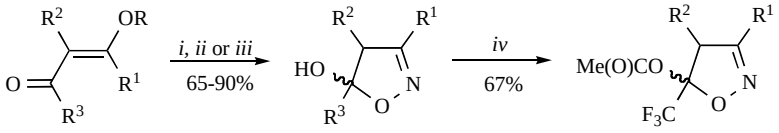
β-Alkoxy halomethyl ketones **28** (in particular, 1,1,1-trihalomethyl-4-alkoxy-3-alken-2-ones) are the (CCC) most used block for the synthesis of 4,5-dihydroisoxazoles. The presence of a halomethyl group in the precursor is a determining factor in the regiochemistry of the reaction. Considering that the rate determination step of the reaction is the Michael type conjugated addition, the nucleophilic nitrogen atom of hydroxylamine attacks exclusively the β-carbon atom of enone, while the oxygen atom attacks carbonyl carbon leading to 5-halomethyl-5-hydroxy-4,5-dihydroisoxazoles **9** regiospecifically [18-20,40,43-48] (Scheme **10**). The β-alkoxy halomethyl ketones **28** have been prepared from the reaction between acetals or enol ethers with haloacyl groups of the type CX_3CO and CHX_2CO, where X = F, Cl [18,20,45,46].



Scheme 9.

In 2001, Martins *et al.* [49] reported an efficient synthetic approach for the preparation of series of 5-heteroalkyl-1,1,1-trichloro-4-metoxy-3-alken-2-one **30** intermediates to regiospecifically obtain 3-heteroalkyl-4,5-dihydroisoxazoles **31**, with regular to good yields (Scheme **11**).

β-Alkoxyvinyl halomethyl ketones derived from dihydrofuran and dihydropyran **33** reacted with hydroxylamine and provided a mixture of 5-halomethyl-5-hydroxy-4,5-dihydroisoxazoles **34** and 3-cyano-2-halomethyl-2-hydroxy-tetrahydrofuran or -tetrahydropyran **32** [20,45] (Scheme **12**). The product ratio was mainly governed by the reaction temperature. Unexpectedly, the 5-dichloromethyl-5-hydroxy-4,5-dihydroisoxazole in the presence of sulfuric acid at 30°C yielded the bicyclic 4,5-dihydroisoxazoles **35** (Scheme **12**) [45]. The formation of these compounds was explained by the acid catalyzed intramolecular dehydration between the two hydroxyl groups. It is noteworthy that the same bicyclic 4,5-dihydroisoxazoles were not obtained when the dichloromethyl group was replaced by a trichloromethyl or trifluoromethyl group at position 5 of the 4,5-dihydroisoxazole ring [20]. The proposed mechanism for obtaining cyano-compounds involves the protonation of the oxygen atom of the isoxazole ring leading to the rupture of the C-O bond, to afford a β-halomethyl ketone oxime. The carbonyl group of this oxime can then undergo an attack from the hydroxyl

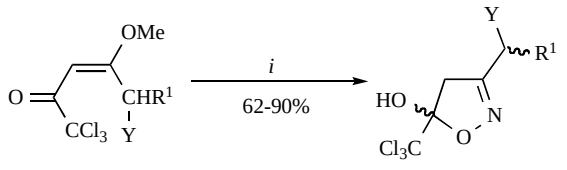


28 **9** **29**

i: $NH_2OH\bullet HCl$, Pyridine, H_2O, 35-52°C, 16-48 h
ii: $NH_2OH\bullet HCl$, Pyridine or HCl, MeOH, 45-70°C, 16 h
iii: $NH_2OH\bullet HCl$, H_2O, THF, r.t.
iv: $(CH_3CO)_2O$, reflux, 5 h

Entry	Method	R^3	R^1	R^2	R	Ref.
1	*i*	$CHCl_2$	H	H	Et	[45]
2	*i*	$CHCl_2$	Me	H	Me	[45]
3	*i*	CCl_3	H	H	Et	[19,20]
4	*i*	CCl_3	Me	H	Me	[20]
5	*i*	CCl_3	H	Me	Et	[20]
6	*ii*	CCl_3	H	Et	Me	[72]
7	*ii*	CCl_3	Ph	H	Me	[46]
8	*ii*	CCl_3	Me-4-Ph	H	Me	[46]
9	*ii*	CCl_3	MeO-4-Ph	H	Me	[46]
10	*ii*	CCl_3	F-4-Ph	H	Me	[46]
11	*ii*	CCl_3	Cl-4-Ph	H	Me	[46]
12	*ii*	CCl_3	Br-4-Ph	H	Me	[46]
13	*ii*	CCl_3	NO_2-4-Ph	H	Me	[46]
14	*ii*	CCl_3	Et	Me	Me	[72]
15	*ii*	CCl_3	Ph	Me	Me	[72]
16	*i*,*iii*	CF_3	H	H	Et	[40,43,44,20]
17	*iv*	CF_3	H	H	-	[44]
18	*i*	CF_3	Me	H	Me	[40,42,43,19]
19	*ii*	CF_3	*i*-Bu	H	Me	[47]
20	*ii*	CF_3	Ph	H	Me	[46]
21	*ii*	CF_3	Me-4-Ph	H	Me	[46]
22	*ii*	CF_3	MeO-4-Ph	H	Me	[46]
23	*ii*	CF_3	F-4-Ph	H	Me	[46]
24	*ii*	CF_3	Cl-4-Ph	H	Me	[46]
25	*ii*	CF_3	Br-4-Ph	H	Me	[46]
26	*i*	CF_3	H	Me	Et	[20]
27	*i*	CF_2CF_3	H	H	Et	[48]
28	*i*	CF_2CF_3	Me	H	Me	[48]
29	*i*	CF_2CF_3	H	Me	Et	[48]

Scheme 10.



30 **31**

Y = Br, N_3, OPh, SCH_2CO_2Et, SPh, SCN, I
R^1 = H, Me

i = NH_2OH●HCl, Pyridine, MeOH, 68°C, 16 h

Scheme 11.

group of the hydroxyalkyl side chain, resulting in the closure of the ring, where the oxime group is easily dehydrated forming the cyano group [45].

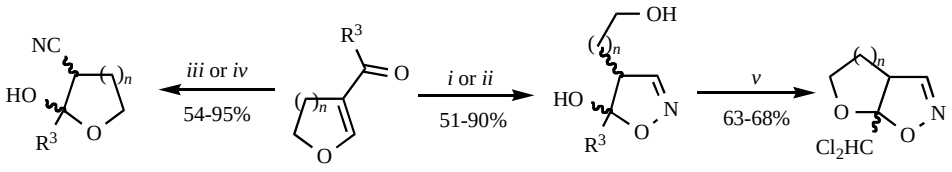
Martins *et al.* [50,51] has investigated alternative methods for the preparation of heterocycles. These authors have proposed the synthesis of 5-trihalomethyl-5-hydroxy-3-alkyl(aryl)-4,5-dihydroisoxazoles **37** by microwave induced techniques using toluene as solvent and ultrasound irradiation in aqueous media (Scheme **13**). These new methods offered several advantages such as: (i) faster reaction rates, (ii) fewer by-products and (iii) higher yields when compared with the *conventional method*.

Martins *et al.* [52] organized a systematic mono- and dibromination of 4-methoxy-1,1,1-trichloro-3-alken-2-ones (**38**) at allylic positions, and demonstrated their application as precursors in the synthesis of heterocycles (Scheme **14**). An interesting example reported was the formation of 3-dibromomethyl-5-hydroxy-5-trichloromethyl-4,5-dihydroisoxazole **39**, including its heterocyclic derivative, 3-formyl-5-hydroxy-5-trichloromethyl-4,5-dihydroisoxazole **40**.

Flores *et al*. published two papers that showed a convenient method to obtain fluorinated and chlorinated 1,3-dielectrophiles derived from 2-acetylthiophene and 2-acetylfuran **41**. The synthesized products, 1,1,1-trifluoro [chloro]methyl-4-methoxy-4-[thien-2-yl]-3-buten-2-ones and 1,1,1-trifluoro[chloro]methyl-4-methoxy-4-[fur-2-yl]-3-buten-2-ones, as well as the products obtained from the hydrolysis, 4,4,4-trihalo-1-[2-heteroaryl]butan-1,3-diones (Entry 5-6), were used to synthesize the new thien-2-yl- and fur-2-yl-dihydroisoxazoles **42** [53,54] (Scheme **15**).

In their investigation on the chemistry of novel heterocycles and their precursors, Martins *et al.* [55,56], using the procedure reported by Hojo *et al.* [57], reacted triethyl orthoacetate **43** with trichloroacetyl chloride in basic media at room temperature, giving 1,1,1-trichloromethyl acetyl ethyl acetate **44** [55] or trihaloacetylketene acetals **46** [56]. These compounds were utilized as building blocks to furnish 3-hydroxy-5-trichloromethyl-4,5-diidroisoxazole **45** and 3-ethoxy-5-polyhalomethyl-4,5-dihydroisoxazoles **47** [55,56] (Scheme **16**). 1,1,1-Trifluoroacetylketene-*O,N*-acetals **48** are easily prepared from the reaction of 1,1,1-trifluoroacetyl-ketene-*O,O*-acetal and amine in the presence of pyridine for 2-6 hours. These precursors also reacted with hydroxylamine hydrochloride to regiospecifically give 5-hydroxy-5-trifluoromethyl-3-amine-4,5-dihydroisoxazoles **49** in good yields [58], (Scheme **16**).

The methyl 10,10,10-trifluoro[chloro]-9-oxo-7-methoxydec-7-enoates **50** were synthesized from the reaction of the respective acetal with trifluoroacetic anhydride or trichloroacetyl chloride. The cyclocondensation reaction of these compounds with hydroxylamine hydrochloride was carried out in hydrochloric acid (or in pyridine) at a molar ratio of 1:1.2:1.2, respectively, using methanol as solvent. The mixture was stirred for 16 h under reflux, to afford the



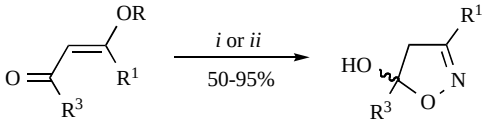
32 **33** **34** **35**

R^3 = $CHCl_2$, $(CH_2)n$OH = 2, 3

i: NH_2OH●HCl, Pyridine, H_2O, 35-52°C, 20-48 h
ii: NH_2OH●HCl, Pyridine, H_2O, 0-20°C, 5h-7 days
iii: NH_2OH●HCl, Pyridine, H_2O, 65-85°C, 3-7 days
iv: H_2SO_4 conc., 50°C, 5-6 h
v: H_2SO_4 conc., 30°C, 5-6 h

Entry	Method	*n*	R^3	$(CH_2)n$OH	Ref.
1	*i,iv*	1	$CHCl_2$	1	[45]
2	*ii,iii*	1	CCl_3	1	[20]
3	*ii,iii*	1	CF_3	1	[20]
4	*i,iv*	2	$CHCl_2$	2	[45]
5	*ii,iii*	2	CCl_3	2	[20]
6	*ii,iii*	2	CF_3	2	[20]

Scheme 12.

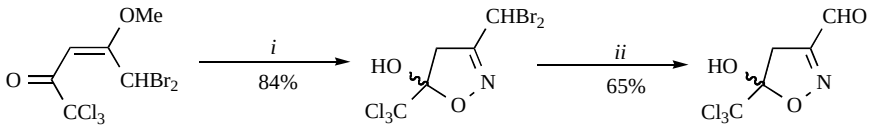


36 **37**

i: NH_2OH•HCl, PhMe, Pyridine, MW, 45 W, 80°C, 6 min
ii: NH_2OH•HCl, Pyridine, H_2O, ultrasound, 45°C, 30 min

Entry	Method	R^3	R^1	R	Ref.
1	*i,ii*	CCl_3	H	Et	[50-51]
2	*i,ii*	CCl_3	Me	Me(Et)	[50-51]
3	*i,ii*	CCl_3	Et	Me(Et)	[50-51]
4	*i ii*	CCl_3	Pr	Me(Et)	[50-51]
5	*i*	CCl_3	*iso*-Pr	Me	[50]
6	*i*	CCl_3	*n*-Bu	Me	[50]
7	*ii*	CCl_3	*iso*-Bu	Et	[51]
8	*i*	CCl_3	*tert*-Bu	Me	[50]
9	*i*	CCl_3	Hexyl	Me	[50]
10	*i*	CCl_3	Ph	Me	[50]
11	*i*	CCl_3	NO_2-4-Ph	Me	[50]
12	*ii*	CF_3	H	Et	[51]
13	*ii*	CF_3	Me	Et	[51]
14	*ii*	CF_3	Et	Et	[51]
15	*ii*	CF_3	Pr	Et	[51]
16	*ii*	CF_3	*iso*-Bu	Et	[51]
17	*ii*	CF_3	*tert*-Bu	Et	[51]
18	*ii*	CF_3	Pentyl	Et	[51]
19	*ii*	CF_3	*iso*-Pentyl	Et	[51]
20	*ii*	CF_3	Hexyl	Et	[51]
21	*ii*	CF_3	Ph	Et	[51]

Scheme 13.

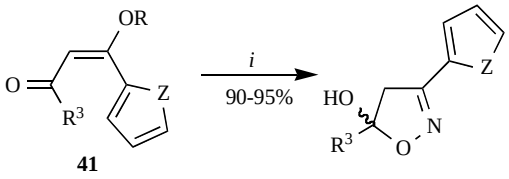


38 **39** **40**

i : NH_2OH•HCl, pyridine, MeOH, 68°C, 16h
ii : AcONa, MeOH, H_2O, 60°C, 24h

Scheme 14.

methyl 6-[-5-trifluoro(chloro)methyl-5-hydroxy-4,5-dihydroisoxazol-3-yl]hexanoates **51** in good yields [59] (Scheme **17**).



41 **42**

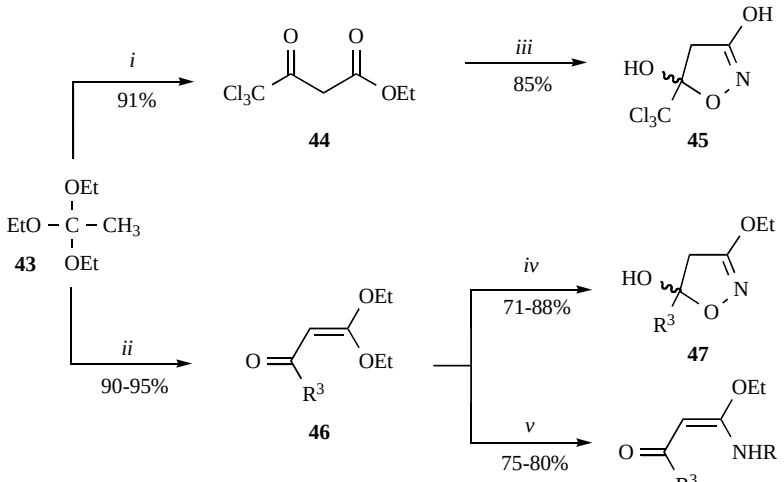
i: $NH_2OH \cdot HCl$, MeOH, 50-65˚C, 8h

Entry	R^3	R	Z	Ref.
1	CCl_3	Me	S	[54]
2	CCl_3	Me	O	[54]
3	CF_3	Me	S	[53,54]
4	CF_3	Me	O	[53,54]
5	CF_3	H	S	[53]
6	CF_3	H	O	[53]

Scheme 15.

In 2005, Martins *et al*. [60] reported the regiospecific synthesis of 1,2-*bis*-(5'-trifluoromethyl-5'-hydroxy-4',5'-dihydroisoxazol-3'-yl) ethane **53** from the cyclocondensation reaction of 1,1,1,10,10,10-hexatrifluoromethyl-4,7-dimethoxydeca-3,7-dien-2,9-dione **52** with hydroxylamine hydrochloride in pyridine and ethanol for 16 h (Scheme **18**).

In 2005, Zanatta *et al.* [61], exploring the synthetic usefulness of a series of trihalomethylated *N*-enonylmethylpyrimidin-2-ones, synthesized the 5-trichloromethyl-5-hydroxy-4,5-dihydroisoxazolylmethyl pyrimidinone. The *N*-enonylmethylpyrimidin-2-one **54** reacted with hydroxylamine hydrochloride in the presence of pyridine, methanol, under reflux for 24 h, furnishing the *N*-methylene-(4,5-dihydroisoxazol-3-yl)pyrimidinone derivative **55** in 80% yield (Scheme **19**). The *N*-enonylmethylpyrimidin-2-ones were also useful intermediates for the synthesis of other heteronucleoside analogues, such as pyrazolyl and benzoimidazolyl derivatives.

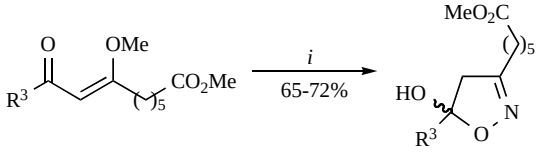


i: CCl_3COCl, pyridine, Et_2O, r.t., 24h
ii: R_3COY, pyridine, CCl_4, r.t, 24h
Y= Cl, $OCOCF_3$, $OCOCF_2CF_3$

iii: $NH_2OH \cdot HCl$, pyridine, H_2O, r.t., 24h
iv: $NH_2OH \cdot HCl$, pyridine, H_2O, 40°C, 24h
v: RNH_2, CH_2Cl_2 or CH_3CN, pyridine, r.t or reflux, 2-6h
vi: $NH_2OH \cdot HCl$, NEt_3, EtOH, 78°C, 24h

Entry	R^3	R	Ref.
1	CCl_3	-	[55]
2	CF_3	-	[56]
3	C_2F_5	-	[56]
4	CF_3	H	[58]
5	CF_3	$C(Me)_2Et$	[58]
6	CF_3	Ph	[58]
7	CF_3	CH_2Ph	[58]
8	CF_3	NH_2-4-Ph	[58]
9	CF_3	NO_2-4-Ph	[58]
10	CF_3	3-methylisoxazol-3-yl	[58]
11	CF_3	CH_2CO_2Et	[58]
12	CF_3	$CH(Ph)CO_2Me$	[58]
13	CF_3	CH(*iso*-Bu)CO_2Et	[58]

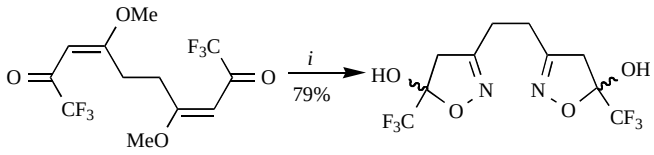
Scheme 16.



50 **51**

i: NH_2OH•HCl, HCl, pyridine, MeOH, 16 h
$R^3 = CCl_3$, CF_3

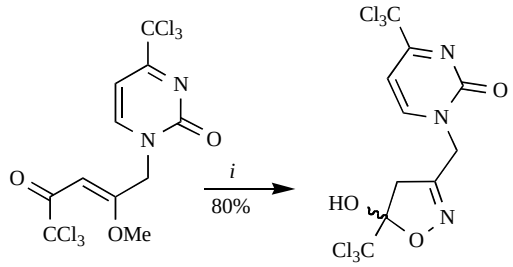
Scheme 17.



52 **53**

i: NH_2OH•HCl, Pyridine, EtOH, reflux, 16h

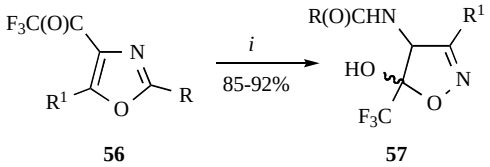
Scheme 18.



54 **55**

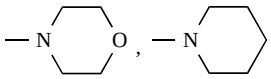
i: NH_2OH•HCl, Pyridine, MeOH, reflux, 24 h

Scheme 19.



56 **57**

R = Ph, NO_2-4-Ph
$R^1 = NMe_2$,



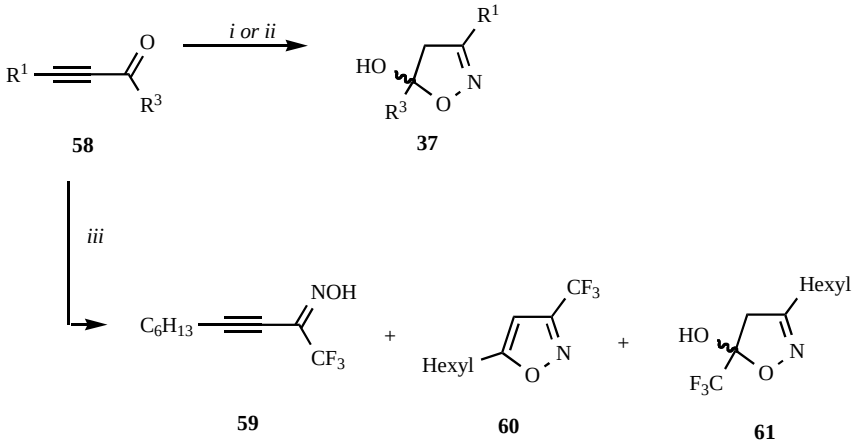
i: NH_2OH, EtOH, 78°C, 1-2 h

Scheme 20.

2.3. Preparation of 4,5-Dihydroisoxazoles from Others Precursors

In 1976, Clerin *et al*. [62] showed an interesting route to synthesize 3-amino-4-acylamino-5-trifluoromethyl-4,5-dihydroisoxazoles **57** from the reaction of 2-aryl-4-trifluoromethyl-5-aminooxazoles **56** with hydroxylamine (Scheme **20**). The reaction was carried out in reflux of ethanol, affording the products in high yields (85-92%). This new route proceeded *via* the nucleophilic attack of the nitrogen atom of hydroxylamine on the 5-position of 5-aminooxazoles.

Trifluoroacetyl acetylene **58** reacted with hydroxylamine hydrochloride, under specific conditions, regiospecifically giving 5-trihalomethyl-4,5-dihydroisoxazoles **36** [63-64] (Scheme **21**). This precursor reacted also in methanol with a catalytic amount of sodium hydroxide affording a mixture of oxime **59**, 3-trifluoromethylisoxazole **60** and 5-trifluoromethyl-5-hydroxy-4,5-dihydroisozaxole **61** at a ratio of 1:2:2.3, respectively [63]. On the other hand, the 5-trifluoromethyl-4,5-dihydroisozaxole **61** was obtained as simple compounds in methanol under reflux, in the presence of sodium methoxyde [63]. Unfortunately, the authors omitted the information about the yield these reactions. Martins *et al*. [64], in a similar procedure, synthesized 3-phenyl-5-trichlo-



58 **37** **59** **60** **61**

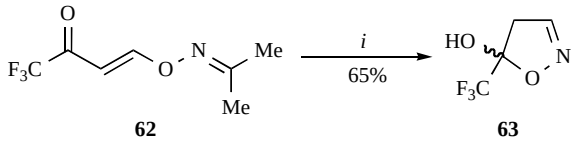
$R^3 = CCl_3$, R^1 = Ph (Ref. [64])
$R^3 = CF_3$, R^1 = Hexyl (Ref. [63])

i: NH_2OH•HCl, MeONa, MeOH, 68°C, 2 hours
ii: NH_2OH•HCl, Pyridine, MeOH, 68°C, 12 hours (70% yield)
iii: NH_2OH•HCl, cat NaOH, MeOH; Product molar ratio obtained: 1(**59**) : 2(**60**) :2.3(**61**)

Scheme 21.

romethyl-5-hydroxy-4,5-dihydroisoxazole **37** in 70% yields, using pyridine instead of sodium methoxyde (Scheme **21**).

4,5-Dihydroisoxazole **63** was obtained from the auto-condensation of (*E*)-*O*-[2-(trifluoroacetyl)vinyl] acetoxime **62** in aqueous $NaHCO_3$, as the only product in 65% yield [65] (Scheme **22**).



62 **63**

i: $NaHCO_3$, H_2O

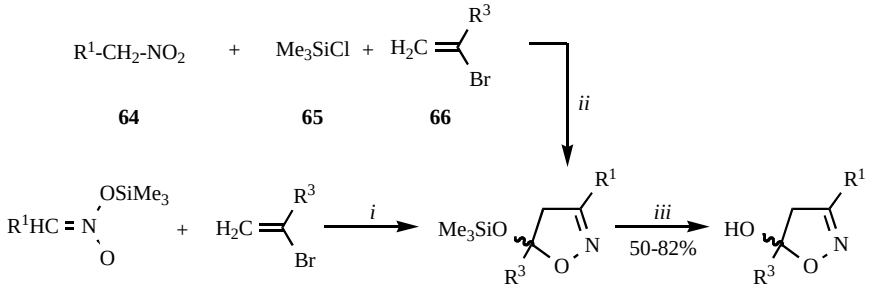
Scheme 22.

Chen *et al*. [66] reported the synthesis of 4,5-dihydroisoxazoles from a 1,3-dipolar cycloaddition reaction. This synthesis consisted of the reaction of trimethylsilyl nitronates **67** and 1-bromo-1-per(poly)-fluoroalkylethenes **65**, in one or two-steps, to regiospecifically give 4,5-dihydroisoxazoles **37**. The intermediate containing the trimethylsiloxy group **68** was also isolated (Scheme **23**).

A Russian group regiospecifically synthesized 5-trifluoromethyl-4,5-dihydroisoxazole **70** from the reaction of trifluoromethyldihydropyrone **69** with hydroxylamine hydrochloride in 62% yield (Scheme **24**) [67].

The reaction of hydroxylamine with trifluoromethyl-chromene-4-thione **71** [68] or 2-hydroxy-2-polyfluoroalkyl-chroman-4-ones **73** [69] regiospecifically afforded 5-polyfluoroalkyl-4,5-dihydroizoxazoles **74**. Trifluoromethyl-chromene-4-thione **71** reacted very smoothly and selectively with hydroxylamine hydrochloride on the thione carbon to form chromone oxime **72** in 72 % yield. Then, the oxime **72** led to the respective 5-trifluoromethyl-5-hydroxy-4,5-dihydroisoxazole **74** in ethanol under reflux in the presence of concentrate HCl [68]. Also, the 2-hydroxy-2-polyfluoroalkylchroman-4-ones **73** reacted with hydroxylamine in the presence of sodium acetate dissolved with heating in aqueous ethanol, and the resulting solution was then refluxed for 1h, to yield the respective 4,5-dihydroisoxazoles **74** (Scheme **25**) [69].

In 2005, Rosa [70] obtained the precursors of β-dimethylaminovinyl ketones from the condensation reaction of *N*,*N*-dimethylformamide dimethyl acetal with several substituted ketones. The study showed that the reaction of trichloromethyl substituted β-dimethylaminovinyl ketone **76** with hydroxylamine hydrochloride regiospecifically led to 5-trichlorometyl-4,5-dihydroisoxazole **26** (Scheme **26**).

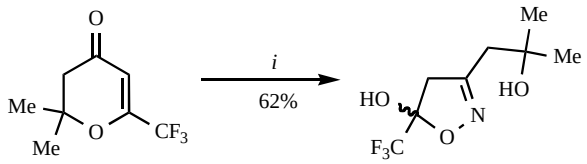


64 **65** **66** **67** **66** **68** **37**

i: PhH, Et_3N, 30-40°C, 2 days
ii: PhH, Et_3N, 30-40°C, 2 days
iii: PhH, *p*-TsOH, 30-40°C, 2 h

Entry	Methods	R^3	R^1	Ref.
1	*ii, iii*	CF_3	Me	[66]
2	*i, iii*	CF_3	Et	[66]
3	*ii, iii*	CF_3	Et	[66]
4	*ii, iii*	CF_2CF_2Br	Me	[66]
5	*ii, iii*	CF_2CF_2Br	Et	[66]
6	*i, iii*	$(CF_2)_3CF_2Cl$	Me	[66]
7	*ii, iii*	$(CF_2)_3CF_2Cl$	Me	[66]
8	*ii, iii*	$(CF_2)_3CF_2Cl$	Et	[66]
9	*i, iii*	$(CF_2)_5CF_2Cl$	Me	[66]
10	*ii, iii*	$(CF_2)_5CF_2Cl$	Et	[66]

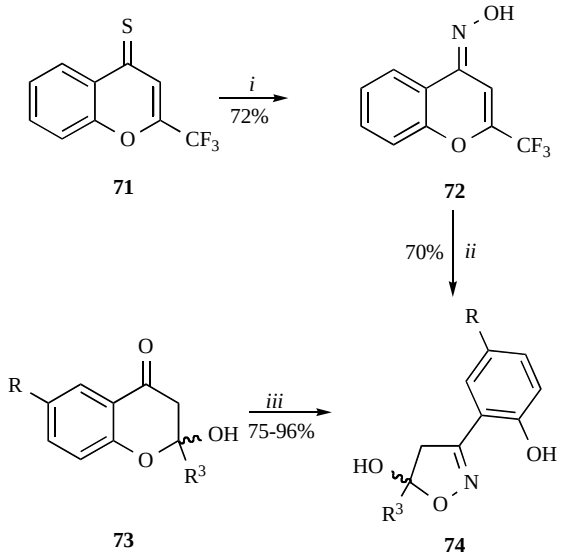
Scheme 23.



69 **70**

i: $NH_2OH \cdot HCl$

Scheme 24.



71 **72** **73** **74**

$R^3 = CF_3$ R = H (Refs. [68], [69])

$R^3 = CF_3$, CF_2CF_2H, CF_2H R = H, Me (Ref. [68])

i: $NH_2OH \cdot HCl$, KOH, EtOH, 20°C, 5min

ii: EtOH, HCl, reflux, 1h

iii: $NH_2OH \cdot HCl$, AcONa, EtOH, H_2O, reflux, 1h

Scheme 25.

In 2005, Chesworth *et al*. [71], interested in new heterocyclic ligands for the estrogen β-receptor, synthesized 5-hydroxy-5-trifluoromethyl-3-(4-methoxyphenyl)-4-phenyl-4,5-dihydroisoxazole **78** from the acylation of the dianion of 1-(4-methoxy-phenyl)-2-phenylethanone oxime **77** with trifluoroacetic acid ethyl ester. The dianion was generated using BuLi as base. Unfortunately, the authors omitted other information about the reaction, such as yield, time and temperature (Scheme **27**).

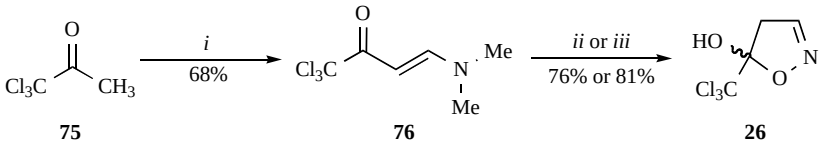
3. NMR SPECTROSCOPY

The NMR data listed in the **Supplementary Material** were collected from the literature and correspond to the period ending in 2006. If some references are more recent, they correspond to results that were available to us during the elaboration of this manuscript. A number of data, referred to as 'This work' in the tables, are being reported here for the first time. The NMR data presented in the tables are ordered according to the ring substitution pattern: *(i)* for the halomethylated group (R^3), from the dichloromethyl, trichloromethyl, trifluoromethyl and polyfluoroalkylated groups; *(ii)* for R^2 and R^1 groups, from the non-substituted, alkyl, aryl, heteraryl, heteralkyl and 3,4-disubstituted compounds.

3.1. ^{13}C NMR Chemical Shifts

The ^{13}C NMR chemical shifts of the 109 different 5-halomethyl-5-hydroxy-4,5-dihydroisoxazoles reported in the literature are listed in the **Supplementary Material**. From the total compounds, it was possible to divide them into 5-dichloromethyl-substituted (5), 5-trichloromethyl-substituted (48), 5-trifluoromethyl-substituted (59) and 5-polyfluoroalkyl-substituted (9).

In order to systematize the ^{13}C NMR data depicted in the **Supplementary Material**, histograms were drawn for the ^{13}C chemical shifts of the reported compounds (Fig. **3**). To draw the histograms, each compound was considered once



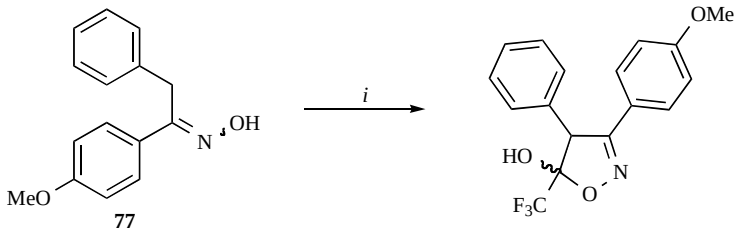
75 **76** **26**

i: DMFDMA, $BF_3 \cdot OEt_2$, PhMe, 115°C, 24 h

ii: $NH_2OH \cdot HCl$, EtOH, Pyridine, 78°C, 16h (76% yield)

iii: $NH_2OH \cdot HCl$, EtOH, 78°C, 16h (81%)

Scheme 26.



77 **78**

i: BuLi, CF_3CO_2Et

Scheme 27.

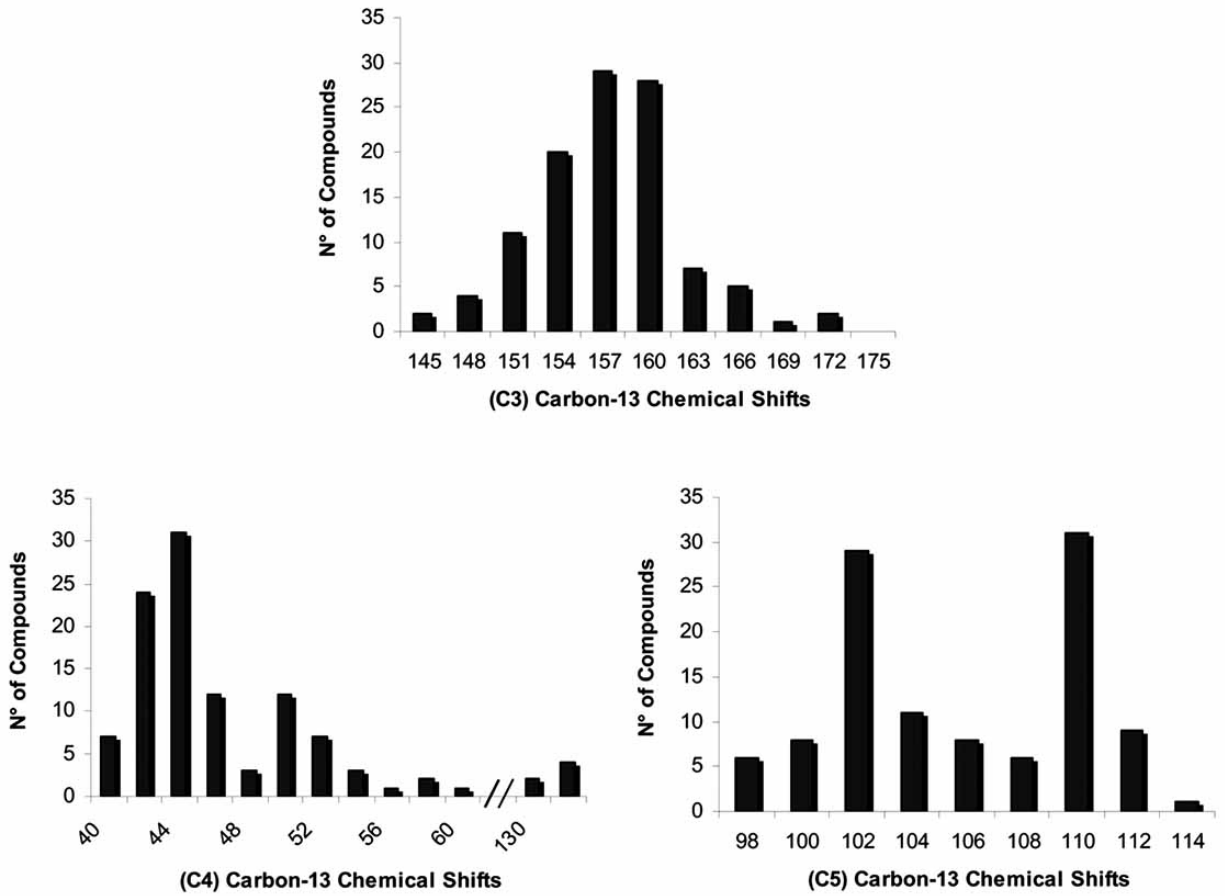


Fig. (3). Histograms of the C3, C4 and C5 chemical shifts (in ppm) of 4,5-dihydroisoxazoles.

(for compounds that appear several times in the **Supplementary Material** in association with different authors or different solvents). The histograms of Fig. (**3**) show that the ^{13}C chemical shift data of the reported 4,5-dihydroisoxazoles are distributed over a range of 30 ppm (C3), 24 ppm (C4) and 16 ppm (C5). The C3 shows an average chemical shift of 157 ppm, which makes it possible to place more than 70% of the reported chemical shifts in a range of ±3.0 ppm from this value. The C4 shows an average chemical shift of 44 ppm, which makes it possible to place more than 60% of the reported chemical shifts in a range of ±2.0 ppm from this value. The compounds substituted at the 4-position with the 4-fluorophenyldiazo group show, for this carbon, an average chemical shift of 132 ppm. The C5 exhibits two sets of average chemical shifts: one at 102 ppm, with 44% of the reported chemical shifts in a range of ±2.0 ppm from this value; and the other at 110 ppm, with 42% of the chemical shifts in a range of ±2.0ppm from this value. The C6 exhibits four sets of average chemical shifts: 70 ppm with the $CHCl_2$ substituent, 100 ppm with CCl_3, 120 ppm with CF_3 and 110 ppm with the polyfluoroalkyl group.

In addition, empirical additive substituent increments were determined from the experimental data, (Equations **1-4** and Table (**1**)). These additive increment data can be used to predict the ^{13}C chemical shift of the 4,5-dihydroisoxazoles, (Equations (**5-8**)).

To calculate the contributions of the Substituent Chemical Shift (SCS) of different substituents, we assumed that these contributions were additive. The first step was to browse through the table to look up and eliminate those substituents that appeared only once or that presented some doubt about their assignment. The resulting set was examined and compounds for which not all chemical shifts are known were excluded. Thus, from the ^{13}C NMR experimental data of 4,5-dihydroisoxazoles, the SCS increments were determined, taking non- and di-substituted 5-trichloromethyl-5-hydroxy-4,5-dihydroisoxazoles as references. The SCS increments are indicated by Greek letters according to the ring position occupied by this substituent relative to a given carbon. These increments were determined by the substitution of the system of Equations (**1-4**).

$$\alpha_n(\text{ppm}) = [\delta_{c\text{-}n}(\alpha_R C\text{-}n) - \delta_{c\text{-}n}(\text{REF})] \quad (\mathbf{1})$$

$$\beta_n(\text{ppm}) = [\delta_{c\text{-}n}(\beta_R C\text{-}m) - \delta_{c\text{-}n}(\text{REF})] \quad (\mathbf{2})$$

$$\gamma_n(\text{ppm}) = [\delta_{c\text{-}n}(\gamma_R C\text{-}m) - \delta_{c\text{-}n}(\text{REF})] \quad (\mathbf{3})$$

$$\delta_n(\text{ppm}) = [\delta_{c\text{-}n}(\delta_R C\text{-}m) - \delta_{c\text{-}n}(\text{REF})] \quad (\mathbf{4})$$

In Equation (**1**), α_n is the effect of the alpha substituent on carbon *n*, i.e. the effect of R^1, R^2, R^3 and halogen on C-3, C-4, C-5 and C-6, respectively. $\delta_{c\text{-}n}(\alpha_R C\text{-}n)$ is the chemical shift of alpha-substituted carbon *n*, and $\delta_{c\text{-}n}(\text{REF})$ is the chemical shift of carbon *n* of the reference compound. In Equations (**2-4**), β_{mn}, γ_{mn} and δ_{mn} are the effects of substitu-

ents bound to a carbon *m*, in the beta, gamma and delta positions, respectively; relative to the carbon *n*; *n* and *m* are whole numbers that in the case of the compounds studied in this work. $\delta_{c\text{-}n}$(β, γ or δ_RC-*m*) is the chemical shift of the carbon *n* that has a substituent on carbon *m*, which could be in a beta, gamma or delta position relative to carbon *n*. The parameters determined from Equations (**1-4**) are reported in Table **1**.

Thus, for the ^{13}C chemical shift determinations of C-3, C-4, C-5 and C-6 of the 5-halomethyl-5-hydroxy-4,5-dihydroisoxazoles, a system of equations that use the data determined from the Equations (**5-8**) was elaborated.

$$\delta_{C\text{-}3} = 148.4 + \alpha_3 + \beta_{43} + \gamma_{53} \quad (\mathbf{5})$$

$$\delta_{C\text{-}4} = 45 + \alpha_4 + \beta_{34} + \beta_{54} \quad (\mathbf{6})$$

$$\delta_{C\text{-}5} = 109.3 + \alpha_5 + \beta_{45} + \gamma_{35} \quad (\mathbf{7})$$

$$\delta_{C\text{-}6} = 101.7 + \alpha_6 + \gamma_{46} + \delta_{36} \quad (\mathbf{8})$$

Equations (**5-8**) allow one to estimate with high precision the ^{13}C chemical shift of carbons 3, 4, 5 and 6 for the compounds. The estimated ^{13}C chemical shifts for compounds from Equations (**5-8**) showed high accuracy. The overall quality of the models is indicated by the correlation coefficient, *r*, and r^2 and by the standard error of regression, *SE*. In these models, the values in parentheses represent the standard error of the coefficients (Equations (**9-12**)).

Table 1. Empirical Parameters (ppm) for Equations (5-8)

Subst. R[1]	α_3 (C-3)	β_{34} (C-4)	γ_{35} (C-5)	δ_{36} (C-6)
H	0	0	0	0
Me	8.3	2.3	1.3	0.1
Et	13.3	2.1	2.4	1
Pr	12.1	2.2	2.3	1
-$(CH_2)_4$-	7.8	2.3	1.3	0.1
iso-Bu	11.6	2.2	2.3	1.1
tert-Bu	18.5	-0.6	2.3	0.7
Hexyl	12.3	2.4	2.3	1.1
$(CH_2)_5CO_2Me$	12.1	1.4	1.6	-0.3
OEt	16.5	-4	1.1	-0.1
Ph	8.9	0.3	3.5	0.8
Me-4-Ph	11.5	0.3	3.2	0.7
OMe-4-Ph	9	0.3	3	0.7
F-4-Ph	8.8	0.2	3.5	0.6
Cl-4-Ph	8.9	0.1	3.7	0.6
Br-4-Ph	8.8	-0.2	3.5	0.4
NO_2-4-Ph	8.7	0.4	4.2	0.3
Subst. R^2	β_{43} (C-3)	α_4 (C-4)	β_{45} (C-5)	γ_{46} (C-6)
H	0	0	0	0
Me	5.4	4.6	0.9	2.1
-$(CH_2)_4$-	5.4	5.4	-1.6	0.2
$(CH_2)_2OH$	2.5	6.2	0.7	0.5
$(CH_2)_3OH$	3.6	7.9	0	1.1
Subst. R^3	γ_{53} (C-6)	β_{54} (C-3)	α_5 (C-5)	α_6 (C-6)
CCl_3	0	0	0	0
$CHCl_2$	-0.8	-0.9	-2.8	-28.7
CF_3	-0.5	-1.5	-7.8	21
CF_2CF_3	1.1	0	-6.6	9.3
$(CF_2)_3CF_2H$	-0.8	-6.1	-3.8	6.9
$(CF_2)_5CF_3$	-0.7	-6.1	-3.6	4.7

$$\delta_{C\text{-}3\ (exp.)} = 0.991(\pm 0.02)\ \delta_{C\text{-}3\ (calc.)} + 1.492(\pm 3.00)\ (n = 48,\ r = 0.992,\ r^2 = 0.983,\ SE = 0.62) \quad (\mathbf{9})$$

$$\delta_{C\text{-}4\ (exp.)} = 1.030(\pm 0.03)\ \delta_{C\text{-}4\ (calc.)} - 1.586(\pm 1.22)\ (n = 48,\ r = 0.985,\ r^2 = 0.971,\ SE = 0.59) \quad (\mathbf{10})$$

$$\delta_{C\text{-}5\ (exp.)} = 1.027(\pm 0.02)\ \delta_{C\text{-}5\ (calc.)} - 3.009(\pm 2.61)\ (n = 48,\ r = 0.987,\ r^2 = 0.975,\ SE = 0.64) \quad (\mathbf{11})$$

$$\delta_{C\text{-}6\ (exp.)} = 0.970(\pm 0.01)\ \delta_{C\text{-}6\ (calc.)} + 2.943(\pm 0.76)\ (n = 48,\ r = 0.999,\ r^2 = 0.998,\ SE = 0.74) \quad (\mathbf{12})$$

All the models showed remarkable correlation. The substituent empirical increments were able to explain > 97.9% of the variability of the ^{13}C chemical shifts of these 4,5-dihydroisoxazoles compounds. The experimental and calculated ^{13}C chemical shifts of the 4,5-dihydroisoxazoles showed an excellent linear co-relationship analysis for the compounds studied (Equation (**13**)).

$$\delta_{cal.} = 1.001(0.001)\ \delta_{exp.} - 0.225(0.140)\ (r = 1.0,\ SE = 0.695) \quad (\mathbf{13})$$

3.2. ^{17}O and ^{15}N NMR Chemical Shifts

Although oxygen is an important atom in organic chemistry, there are few systematic studies on ^{17}O NMR chemical shifts in heterocyclic compounds in the literature [74,75]. Despite experimental difficulties in obtaining a good sensitivity spectrum for ^{17}O nuclei that combine both low natural abundance and a low gyromagnetic ratio, with the new development of NMR equipment, it is possible to acquire a ^{17}O NMR spectrum in less than an hour since reasonably concentrated samples are relatively easy to achieve with small molecules of organic compounds [73-87]. Despite the line broadening caused by the quadrupolar moment of the ^{17}O nucleus, due to the nature of its 5/2 spin, it is possible to acquire spectra with a reasonable line width, which allows the assignment of the chemical shifts of this nucleus with an accuracy of ±1-2 ppm, that is, an error of 0.1-0.2% or an accuracy ten to twenty times lower than that for the ^{13}C nucleus. However, this lack of accuracy of the ^{17}O chemical shift is negligible if one considers the high sensitivity of this nucleus to electronic and spatial effects (with a spectral width greater than 800 ppm). It is noteworthy to address the issues of precision and reproducibility of the ^{17}O chemical shifts. Although modern NMR equipments have a high digital resolution, greater than 0.01 ppm, this is minor considering the line width for the ^{17}O NMR signal ($\Delta\nu_{½}$ > 5 ppm). Thus, most authors report ^{17}O chemical shifts with one (or two) significant figure(s) after the decimal point. However, if two authors record the spectrum of the same compound under the same conditions (in general: the same solvent, temperature and at approximately the same concentration), their chemical shifts can often differ by more than 1.0 ppm due to variations in concentration, temperature, quality of solvents, solubility, viscosity of the solution and water content, etc. Our reason for using an accuracy of ±0.1 ppm is necessitated by the high resolution of modern spectrometers, which allows two signals to be distinguished when they are separated by less then 1.0 ppm. Thus, from our observations [60,67], the major problem reported with ^{17}O NMR chemical shifts has been their reproducibility.

The ^{15}N nuclei present a natural abundance (0.37%), ten times greater then that of ^{17}O nuclei, and present low sensitivity (0.00104 in relation to ^{1}H, in a constant magnetic field). However, because the ^{15}N presents a magnetic moment similar to that of ^{1}H (I = ½) and due to the new development of NMR equipment with multinuclear pulses and high sensitivity probes, it is possible to obtain ^{15}N NMR data in natural abundance with good signal resolution. In these spectra, it is possible to observe the N-H coupling with one, two or three bond distances [82]. In addition, polarization transference pulse techniques, e.g., INEPT, DEPT or SPT, have been developed and allow for the easy acquisition of ^{15}N NMR data for heterocycles [82-85].

The ^{17}O and ^{15}N NMR chemical shift data of 4,5-dihydroisoxazoles reported in the literature is quite rare. In fact,, all the chemical shifts present in this review are from our work group. Martins *et al.* has also shown a quantitative relationship between the torsion angle and the solvent effects on the ^{17}O chemical shifts in 5-trichloromethyl-5-hydroxy-4,5-dihydroisoxazoles [73,86]. The lack of data for ^{17}O and ^{15}N NMR may be explained by experimental difficulties in obtaining a good sensitivity spectrum for these nuclei that combine both low natural abundance and a low gyromagnetic ratio. In the **Supplementary Material**, the ^{17}O and ^{15}N chemical shifts of 4,5-dihydroizoxazoles are listed.

Although the sampling is very small, the data shown in Table (**2**) exhibit the additive effect of the substituents present on the 4,5-dihydroisoxazole ring. This allowed us to write Equations (**14-15**).

$$\delta O1 = 253.9 + \gamma_{31} + \gamma_{41} \quad (\mathbf{14})$$

$$\delta OH = 67.1 + \gamma_{4OH} + \delta_{OH} \quad (\mathbf{15})$$

Although the ^{15}N chemical shift data of 4,5-dihydroisoxazoles are also reduced, it is possible to observe that the alkyl(aryl) groups on C-3 have a shielding effect compared to the signal of the nonsubstituted 5-trichloromethyl-5-hydroxy-4,5-dihydroisoxazoles. Equation (**16**) exhibits the additive effect of the substituents on the ^{15}N chemical shifts.

$$\delta N2 = 379.2 + \beta_{32} + \gamma_{42} \quad (\mathbf{16})$$

3.3. ^{19}F NMR Chemical Shifts

Considering the nucleides belonging to Main Group 7 of the Periodic Table, ^{19}F is by far the most important for the determination of structure by NMR spectroscopy, and, therefore, is of great significance in applications in physical chemistry and biology. For example, the comparative analysis of ^{19}F NMR data for the 5-R^F-substituent and 3-R^F-substituent in the azole rings revealed some of their spectral features, making a clear-cut distinction between the two compounds possible. In addition, the utilization of ^{19}F NMR data has been found to be a method for assigning whether the

Table 2. The ^{17}O and ^{15}N Substituent Chemical Shifts (SCS) on the 4,5-Dihydroisoxazole Ring

Substituent			O-1	OH	N-2
R^3	R^2	R^1	γ_{31}	δ_{3OH}	β_{32}
CCl_3	H	H	0	0	0
CCl_3	H	Me	-7,3	0,5	-14
CCl_3	H	Et	-8,6	0,6	-15
CCl_3	H	Pr	-8,5	1,1	-13,3
CCl_3	H	*iso*-Pr	-10,8	0,9	-14,8
CCl_3	H	*cyclo*-Pr	-10,5	0,8	-
CCl_3	H	*iso*-Bu	-7,6	0,8	-12,9
CCl_3	H	*tert*-Bu	-11,3	0,6	-12,8
CCl_3	H	CH_2Br	-3,6	1,2	-6
CCl_3	H	$CHBr_2$	-2,7	2,3	-7,1
CCl_3	H	Ph	-3,9	1,6	-9,4
			γ_{41}	γ_{4OH}	γ_{42}
CCl_3	Me	H	-0,3	-11,4	4,6
CCl_3	Et	H	6,5	-5,8	-20,5
			$\gamma_{31} + \gamma_{41}$	$\delta_{3OH} + \gamma_{4OH}$	$\beta_{32} + \gamma_{42}$
CCl_3	Me	Et	-12,2	-11,8	-20,5
CCl_3	Me	Ph	-2,2	-3	-15,6
CCl_3	$-(CH_2)_4-$		-10,7	-8,9	-3,8
CCl_3	$-(CH_2)_5-$		-9,4	-10,1	-3,8

trifluoromethyl group is attached on a saturated carbon (non-aromatic heterocyclic ring) or on an unsaturated carbon (aromatic heterocyclic ring). In the **Supplementary Material**, the 5-halomethyl-5-hydroxy-4,5-dihydroisoxazoles containing ^{19}F chemical shifts reported in the literature are shown. The main problem in the ^{19}F NMR data presented in the literature is related to the use of different references to establish the chemical shifts. The reports used trifluoroacetic acid [65], halomethane [27,30,33,66] or fluorobenzene [34] as the reference.

4. ACKNOWLEDGEMENTS

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SUPPLEMENTARY MATERIAL

5-Halomethyl-5-Hydroxy-4,5-Dihydroisoxazoles: Synthesis and ^{13}C, ^{17}O, ^{15}N, ^{19}F NMR Spectroscopy

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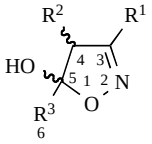
List of Contents

I. ^{13}C NMR chemical shifts of 4,5-dihydroisoxazoles (S2)

II. ^{17}O and ^{15}N NMR chemical shifts of 4,5-dihydroisoxazoles (S5)

III. ^{19}F NMR chemical shifts of 4,5-dihydroisoxazoles (S6)

Table A. ^{13}C NMR Chemical Shifts of 4,5-dihydroisoxazoles



Substituents			δ ^{13}C				NMR Conditions	Refs.
R^3	R^2	R^1	C-3	C-4	C-5	C-6		
$CHCl_2$	H	H	147.6	44.1	106.5	73.0	*a*	[45,72]
$CHCl_2$	H	Me	157.3	46.1	107.6	72.9	*a*	[45,72]
$CHCl_2$	$(CH_2)_2OH$	H	151.0	50.1	106.8	74.4	*a*	[45,72]
$CHCl_2$	$(CH_2)_3OH$	H	151.8	53.2	107.1	75.5	*a*	[45,72]
$CHCl_2$	$-(CH_2)_4-$		161.3	51.8	106.0	74.0	*a*	[72]
CCl_3	H	H	148.4	45.0	109.3	101.7	*a*	[20,50,51,70,72]
CCl_3	H	Me	156.7	47.3	110.6	101.8	*a*	[20,29,50,51,72]
CCl_3	H	Et	161.7	47.1	111.7	102.7	*b*	[50,51]
CCl_3	H	Pr	160.5	47.2	111.6	102.7	*b*	[50,51]
CCl_3	H	*iso*-Pr	164.7	45.3	111.6	102.8	*b*	[50]
CCl_3	H	*cyclo*-Pr	162.5	45.4	111.6	102.7	*b*	[50]
CCl_3	H	Bu	160.7	45.4	111.6	102.7	*b*	[50]
CCl_3	H	*iso*-Bu	160.0	47.2	111.6	102.8	*b*	[50,51]
CCl_3	H	*tert*-Bu	166.9	44.4	111.6	102.4	*b*	[50]
CCl_3	H	Hexyl	160.7	47.4	111.6	102.8	*b*	[50]
CCl_3	H	$(CH_2)_5CO_2Me$	160.5	46.4	110.9	101.4	*c*	[59]
CCl_3	H	CHO	159.4	40.4	114.4	100.4	*c*	[52]
CCl_3	H	CH_2Br	157.3	44.7	112.9	102.0	*c*	[52]
CCl_3	H	$CHBr_2$	158.6	42.6	113.7	101.4	*c*	[52]
CCl_3	H	CH_2N_3	156.0	44.2	111.4	100.6	*c*	[49]
CCl_3	H	CH_2OPh	156.7	43.7	111.8	100.3	*c*	[49]
CCl_3	H	$CH_2SCH_2CO_2Et$	158.5	44.4	111.3	100.5	*c*	[49]
CCl_3	H	CH_2SPh	157.4	43.6	111.1	99.6	*c*	[49]
CCl_3	H	CH_2SCN	155.7	40.0	111.9	101.5	*c*	[49]
CCl_3	H	CH_2I	156.5	47.7	110.7	101.0	*c*	[49]
CCl_3	H	CH(Me)Br	161.1	42.2 41.9	110.9 110.7	101.7 101.5	*c*	[49]
CCl_3	H	$CH(Me)N_3$	159.4 159.5	43.0 42.6	111.2	100.4 100.5	*c*	[49]

(Table A). contd…..

Substituents			δ ^{13}C				NMR Conditions	Refs.
R^3	R^2	R^1	C-3	C-4	C-5	C-6		
CCl_3	H	CH(Me)OPh	160.1	42.1	110.6	100.7	*c*	[49]
CCl_3	H	CH(Me)SCH_2CO_2Et	159.9	42.4 42.7	111.6	100.6	*c*	[49]
CCl_3	H	CH(Me)SPh	160.7	43.3	111.4	101.2	*c*	[49]
CCl_3	H	CH(Me)SCN	157.0 157.1	42.0 42.6	111.3	100.2	*c*	[49]
CCl_3	H	CH(Me)I	161.6	45.9	110.5 110.1	100.6	*c*	[49]
CCl_3	H	OH	171.5	41.3	109.4	101.8	*b*	[55]
CCl_3	H	OEt	164.9	41.0	110.4	101.6	*b*	[55]
CCl_3	H	Ph	157.3	45.3	112.8	102.5	*b*	[29,50]
CCl_3	H	Ph	158.0	45.2	112.7	102.4	*d*	[46]
CCl_3	H	Me-4-Ph	159.9	45.3	112.5	102.4	*d*	[46]
CCl_3	H	OMe-4-Ph	157.4	45.3	112.3	102.4	*d*	[46]
CCl_3	H	F-4-Ph	157.2	45.2	112.8	102.3	*d*	[46]
CCl_3	H	Cl-4-Ph	157.3	45.1	113.0	102.3	*d*	[46]
CCl_3	H	Br-4-Ph	157.2	44.8	112.8	102.1	*d*	[46]
CCl_3	H	NO_2-4-Ph	157.1	45.4	113.5	102.0	*b*	[46]
CCl_3	$(CH_2)_3OH$	H	152.0	52.9	109.3	102.8	*a*	[20,72]
CCl_3	Me	H	153.8	49.6	110.2	103.8	*a*	[20,72]
CCl_3	Et	H	152.0	56.2	110.2	103.7	*g*	[73]
CCl_3	$(CH_2)_2OH$	H	150.9	51.2	110.0	102.2	*a*	[20,72]
CCl_3	-$(CH_2)_4$-		161.6	53.5	110.2	103.5	*b*	[29,50]
CCl_3	-$(CH_2)_4$-		161.6	52.7	109.0	102.0	*a*	[20,32,72]
CCl_3	-[(CH_2)(CH-*tert*-Bu)CH_2]		161.9	53.4	109.2	102.1	*b*	[29]
CCl_3	-$(CH_2)_5$-		164.8	55.9	109.6	102.2	*b*	[29]
CCl_3	-$(CH_2)_6$-		164.2	54.1	110.2	102.5	*b*	[29]
CCl_3	Me	Et	165.0	50.0	110.9	103.9	*g*	[29,73]
CCl_3	Me	Ph	162.0	47.4	110.8	103.2	*g*	[29,73]
CF_3	H	H	147.9	43.5	101.5	122.7	*a*	[20,72]
CF_3	H	H	146.5	43.8	101.7	123.0	*b*	[51,66]
CF_3	H	Me	156.4	45.7	102.6	122.5	*a*	[20,72]
CF_3	H	Me	156.0	48.4	102.9	124.2	*b*	[51]
CF_3	H	Et	161.3	44.6	102.8	122.1	*b*	[51]
CF_3	H	Pr	159.8	44.9	102.5	122.2	*b*	[51]
CF_3	H	*iso*-Bu	159.0	44.5	102.3	122.6	*b*	[51]
CF_3	H	*iso*-Bu	159.0	44.6	102.6	122.7	*e*	[47]
CF_3	H	*tert*-Bu	166.2	42.0	102.8	121.2	*b*	[51]
CF_3	H	Pentyl	160.3	45.6	103.4	122.3	*b*	[51]
CF_3	H	*iso*-Pentyl	160.0	44.9	102.4	124.0	*b*	[51]
CF_3	H	Hexyl	160.0	44.8	102.3	120.6	*b*	[51]
CF_3	H	$(CH_2)_4CO_2Me$	159.3	44.8	102.6	122.1	*c*	[59]
CF_3	H	NH_2	158.2	43.2	102.6	123.1	*g*	[58]
CF_3	H	$NHC(CH_3)_2Et$	156.0	45.1	101.3	123.8	*g*	[58]
CF_3	H	NH-Ph	154.2	44.1	101.1	122.9	*g*	[58]
CF_3	H	$NHCH_2$-Ph	158.3	43.5	102.8	123.7	*g*	[58]
CF_3	H	NH-Ph-4-NH_2	154.8	44.6	101.7	123.7	*b*	[58]
CF_3	H	NH-Ph-4-NO_2	155.6	45.1	103.2	119.2	*g*	[58]

(Table A). contd…..

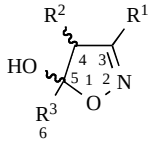
Substituents			δ ^{13}C				NMR Conditions	Refs.
R^3	R^2	R^1	C-3	C-4	C-5	C-6		
CF_3	H	NH(5-methyl-isoxazol-3-yl)	154.3	43.7	103.1	123.6	*b*	[58]
CF_3	H	CH_2CO_2Et	166.2	45.2	103.9	123.3	*g*	[58]
CF_3	H	$CH(Ph)CO_2Me$	157.2	43.3	103.1	123.7	*g*	[58]
CF_3	H	CH(*iso*-Bu)CO_2Et	157.1	42.7	102.2	122.1	*b*	[58]
CF_3	H	OEt	166.0	40.7	103.9	123.2	*b*	[56]
CF_3	H	Ph	157.6	43.1	106.5	123.7	*d*	[46]
CF_3	H	Ph	157.0	42.1	103.5	123.8	*b*	[51]
CF_3	H	Ph	157.7	43.6	104.9	123.6	*a*	[27]
CF_3	H	Ph	156.0	42.0	102.3	120.9	*h*	[30]
CF_3	H	Me-4-Ph	157.6	43.7	104.6	123.6	*d*	[46]
CF_3	H	OMe-4-Ph	157.4	43.1	104.7	123.1	*d*	[46]
CF_3	H	OMe-4-Ph	155.6	43.2	103.2	122.0	*h*	[30]
CF_3	H	F-4-Ph	156.5	42.7	106.8	124.0	*d*	[46]
CF_3	H	F-4-Ph	156.1	43.0	103.5	121.9	*h*	[30]
CF_3	H	Cl-4-Ph	156.9	43.4	105.1	123.4	*d*	[46]
CF_3	H	Cl-4-Ph	155.1	41.8	102.5	120.9	*h*	[30]
CF_3	H	Br-4-Ph	157.0	43.3	105.1	123.5	*d*	[46]
CF_3	H	Br-4-Ph	155.1	41.7	102.5	120.9	*h*	[30]
CF_3	H	NO_2-4-Ph	155.1	41.3	103.5	121.1	*h*	[30]
CF_3	H	Thienyl	153.0	42.8	103.7	122.4	*b*	[53]
CF_3	H	Furyl	148.7	42.5	103.6	122.6	*b*	[53]
CF_3	Me	H	151.5	46.8	101.7	122.2	*a*	[20,72]
CF_3	$(CH_2)_2OH$	H	151.5	49.2	101.6	122.7	*a*	[20,72]
CF_3	$(CH_2)_3OH$	H	151.6	51.8	101.6	122.7	*a*	[20,72]
CF_3	=N-NH-4-F-Ph	Ph	156.0	132.1	98.4	121.7	*h*	[30]
CF_3	=N-NH-F-4-Ph	OMe-4-Ph	155.1	132.4	98.9	122.1	*h*	[30]
CF_3	=N-NH-F-4-Ph	F-4-Ph	154.5	133.3	99.0	122.1	*h*	[30]
CF_3	=N-NH-F-4-Ph	Cl-4-Ph	155.0	131.3	98.5	121.7	*h*	[30]
CF_3	=N-NH-F-4-Ph	Br-4-Ph	155.1	131.3	98.7	121.7	*h*	[30]
CF_3	=N-NH-F-4-Ph	NO_2-4-Ph	153.3	132.8	99.0	121.4	*h*	[30]
CF_3	HNCOPh	$N(Me)_2$	160.3	61.5	100.6	-	*f*	[60]
CF_3	$-(CH_2)_4-$		161.0	51.3	102.0	122.0	*a*	[31,72]
CF_3	$-(CH_2)_2$-CH(*tert*-Bu)CH_2-		160.9	53.0	109.5	122.5	*b*	[34]
CF_3	-(CH(Br)-CH_2-CH(*tert*-Bu)CH_2-		162.5	53.2	106.7	121.5	*b*	[34]
CF_3	$-(CH_2)_5-$		164.4	55.5	102.7	122.3	*b*	[34]
CF_3	-(CH(Br)-$CH_2)_4-$		163.0	51.3	104.0	121.9	*b*	[34]
CF_3	$-(CH_2)_6-$		162.8	52.4	103.3	122.9	*b*	[34]
CF_3	-(CH(Br)$CH_2)_5-$		162.4	48.9	105.0	121.9	*b*	[34]
CF_3	$-(CH_2)_3$-C(CH-Ph)-		159.9	50.4	103.0	122.7	*c*	[33]
CF_3	$-(CH_2)_3$-C(CH-Ph-4-OMe)-		160.0	50.4	102.9	122.7	*c*	[33]
CF_2CF_2H	$-(CH_2)_3-$		173.3	59.3	104.3	110.1	*c*	[33]
CF_2CF_3	H	H	148.0	44.0	102.7	111.7	*b*	[48]
CF_2CF_3	H	Me	156.4	46.2	103.7	111.4	*b*	[48]
CF_2CF_3	H	OEt	166.0	41.0	103.8	110.9	*b*	[56]

(Table A). contd…..

Substituents			δ ^{13}C				NMR Conditions	Refs.
R^3	R^2	R^1	C-3	C-4	C-5	C-6		
CF_2CF_3	Me	H	152.8	47.0	103.4	112.0	*b*	[48]
$(CF_2)_3CF_3$	-$(CH_2)_3$-		172.4	58.8	104.1	107.0	*c*	[33]
$(CF_2)_3CF_3$	-$(CH_2)_3$-C(CH-Ph-4-NMe_2)-		159.9	50.9	105.6	111.4	*c*	[33]
$(CF_2)_3CF_2H$	-$(CH_2)_4$-		160.8	51.6	105.2	108.9	*c*	[33]
$(CF_2)_5CF_3$	-$(CH_2)_4$-		160.9	51.6	105.4	106.7	*c*	[33]

[a] ^{13}C NMR spectra were recorded on a Bruker AC-80 spectrometer (^{13}C at 20.15 MHz), at 308 K, and a Bruker CXP-300 spectrometer (^{13}C at 75.47 MHz), at 298 K, 0.5 M in $CDCl_3$-d_6 and/or DMSO-d_6 containing 0.1 % TMS as internal reference.
[b] ^{13}C NMR spectra were recorded on a Bruker DPX 400 (^{13}C at 100.62 MHz) in 5 mm sample tubes at 298 K (digital resolution ±0.01 ppm) in $CDCl_3$ containing 0.1 % TMS as internal reference.
[c] ^{13}C NMR spectra were recorded on a Bruker DPX-200 spectrometer (^{13}C at 50.32 MHz), at 298 K, 0.5 M in $CDCl_3$ or DMSO-d_6 containing 0.1 % TMS as internal reference.
[d] ^{13}C NMR spectra were recorded on a Bruker AC-80 spectrometer (^{13}C at 20.15 MHz), at 308 K, in Acetone-d_6 solutions of 0.5 M containing 0.1 % TMS as internal reference.
[e] ^{13}C NMR spectra were recorded on a Bruker DPX-200 spectrometer (^{13}C at 50.32 MHz), at 298 K, 0.5 M in DMSO-d_6 containing 0.1 % TMS as internal reference.
[f] ^{13}C NMR spectra were recorded on Varian XL-100/15 (13C at 25.15 MHz) in DMSO-d_6 containing 0.1 % TMS as internal reference.
[g] ^{13}C NMR spectra were recorded on a Bruker DPX 400 (^{13}C at 100.62 MHz) in 5 mm sample tubes at 298 K (digital resolution ±0.01 ppm) in Acetone-d_6 containing 0.1 % TMS as internal reference TMS solutions.
[h] ^{13}C NMR spectra were recorded on a Bruker DPX 300 (^{13}C at 75 MHz) in 5 mm sample tubes at 298 K (digital resolution ±0.01 ppm) in $CDCl_3$ containing 0.1 % TMS as internal reference.

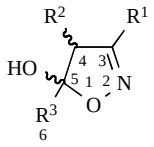
Table B. ^{17}O and ^{15}N NMR Chemical Shifts[a,b] of 4,5-dihydroisoxazoles



Substituent			δ ^{17}O		Refs.	δ ^{15}N	Refs.[c]
R^3	R^2	R^1	O-1	OH		N-2	
CCl_3	H	H	253.9	67.1	[73,87]	379.2	This Work
CCl_3	H	Me	246.6	67.6	[73,87]	365.2	This Work
CCl_3	H	Et	245.3	67.7	[73,87]	364.2	This Work
CCl_3	H	Pr	245.4	68.2	[73,87]	365.9	This Work
CCl_3	H	*iso*-Pr	243.1	68.0	[73,87]	364.4	This Work
CCl_3	H	*cyclo*-Pr	243.4	67.9	[73]	...	This Work
CCl_3	H	*iso*-Bu	246.3	67.9	[73]	366.3	This Work
CCl_3	H	*tert*-Bu	242.6	67.7	[73,87]	366.4	This Work
CCl_3	H	CH_2Br	250.3	68.3	[73,87]	373.2	This Work
CCl_3	H	$CHBr_2$	251.2	69.4	[73,87]	372.1	This Work
CCl_3	H	Ph	250.0	68.7	[73]	369.8	This Work
CCl_3	Me	H	253.6	55.7	[73]	383.8	This Work
CCl_3	Et	H	260.4	61.3	[73]	358.7	This Work
CCl_3	Me	Et	241.7	55.3	[73]	358.7	This Work
CCl_3	Me	Ph	251.7	64.1	[73]	363.6	This Work
CCl_3	-$(CH_2)_4$-		243.2	58.2	[73]	375.4	This Work
CCl_3	-$(CH_2)_5$-		244.5	57.0	[73]	375.4	This Work

[a] ^{17}O NMR spectra were recorded on a Bruker DPX-400 spectrometer, at 54.24 MHz, at 323 K, all spectra were acquired in a 10mm tube, at natural abundance, 2.0 M in MeCN, referenced to external water, in a capillary coaxial tube, δ [$H_2{}^{17}O$]= 0.0 ppm.
[b] ^{15}N NMR spectra were recorded on a Bruker DPX-400 spectrometer, at 40.55 MHz, at 300 K, all spectra were acquired in a 10mm tube, at natural abundance, 2.0 M in THF, referenced to external nitromethane, in a capillary coaxial tube, δ [$MeNO_2$] = 380.2 δ $^{15}NH_3$ = 0.0 ppm).
[c] The references referred to as "This Work" are reported here for the first time.

Table C. ^{19}F NMR Chemical Shifts[a] of 4,5-dihydroisoxazoles



Substituent			δ ^{19}F	Refs.
R^3	R^2	R^1		
CF_3	H	H	-83.7	[66][a]
CF_3	H	Me	5.0	[65][c]
CF_3	H	Et	5.0	[65][c]
CF_3	H	Ph	-80.0	[27][a]
CF_3	H	Ph	-83.4	[30][a]
CF_3	H	OMe-4-Ph	-83.4	[30][a]
CF_3	H	F-4-Ph	-83.0 (CF_3), -109.0 (F-4-Ph)	[30][a]
CF_3	H	Cl-4-Ph	-83.3	[30][a]
CF_3	H	Br-4-Ph	-83.4	[30][a]
CF_3	H	O_2N-4-Ph	-83.5	[30][a]
CF_3	=N-NH-4-F-Ph	Ph	-80.0 (CF_3), -122.0 (=N-NH-4-F-Ph)	[30][a]
CF_3	=N-NH-F-4-Ph	OMe-4-Ph	-80.0 (CF_3), -121.0 (=N-NH-4-F-Ph)	[30][a]
CF_3	=N-NH-F-4-Ph	F-4-Ph	-80.0 (CF_3), -110.0 (F-4-Ph), -121.0 (=N-NH-4-F-Ph)	[30][a]
CF_3	=N-NH-F-4-Ph	Cl-4-Ph	-80.0 (CF_3), -120.0 (=N-NH-4-F-Ph)	[30][a]
CF_3	=N-NH-F-4-Ph	Br-4-Ph	-80.0 (CF_3), -120.0 (=N-NH-4-F-Ph)	[30][a]
CF_3	=N-NH-F-4-Ph	NO_2-4-Ph	-81.0 (CF_3), -122.0 (=N-NH-4-F-Ph)	[30][a]
CF_3	-$(CH_2)_2$-CH(*tert*-Bu)CH_2-		-80.6	[34][b]
CF_3	-(CH(Br)-CH_2-CH(*tert*-Bu)CH_2-		-81.4	[34][b]
CF_3	-$(CH_2)_5$-		-82.2	[34][b]
CF_3	-(CH(Br)-$CH_2)_4$-		-81.5	[34][b]
CF_3	-$(CH_2)_6$-		-82.0	[34][b]
CF_3	-(CH(Br)$CH_2)_5$-		-81.4	[34][b]
CF_3	-$(CH_2)_3$-C(CH-Ph)-		-81.6	[33][a]
CF_3	-$(CH_2)_3$-C(CH-C_6H_4-4-OMe)-		-81.5	[33][a]
CF_2CF_2H	-$(CH_2)_3$-		-129.0, -131.4, -138.2, -140.7	[33][a]
CF_2CF_2H	-$(CH_2)_4$-		-137.9, -131.1, -129.6	[33][a]
$(CF_2)_3CF_2H$	-$(CH_2)_4$-		-123.9, -121.5, -123.5, -131.3, -139.6	[33][a]
$(CF_2)_3CF_3$	-$(CH_2)_3$-		-127.6, -126.6, -123.0, -122,6, -124.0, -118.6, -81.6	[33][a]
$(CF_2)_3CF_3$	-$(CH_2)_3$-C(CH-C_6H_4-4-NMe_2)-		-127.5, -126,6, -122.0, -120.3, -122.2, -81.6	[33][a]
$(CF_2)_5CF_3$	-$(CH_2)_4$-		-127.3, -123.9, -123.2, -121.7, -123.6, -121.1, -81.8	[33][a]
CF_2CF_2Br	H	Me	40.0, -16.5	[65][c]
CF_2CF_2Br	H	Et	40.0, -16.0	[65][c]
$(CF_2)_3CF_2Cl$	H	Me	44.0, 42.0, -9.0	[65][c]
$(CF_2)_3CF_2Cl$	H	Et	44.0, 43.0, -8.3	[65][c]
$(CF_2)_3CF_2Cl$	H	Me	44.0, 42.0, -10.0	[65][c]
$(CF_2)_5CF_2Cl$	H	Et	44.0, 43.0, -10.0	[65][c]

[a] ^{19}F NMR spectra were recorded at 56.4, 89.35 or 376 MHz, CCl_3F as external reference.
[b] ^{19}F NMR spectra were recorded at 376 MHz, C_6H_5F as external reference.
[c] ^{19}F NMR spectra were recorded at 56.4 MHz in $CDCl_3$ using CF_3CO_2H as external reference.