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FLUORINATED HETEROCYCLIC COMPOUNDS. SYNTHESIS OF 5-AMINO-, 5-*N*-ALKYLAMINO-, AND 5-*N*,*N*-DIALKYLAMINO-3-PERFLUOROHEPTYL-1,2,4-OXADIAZOLES

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Abstract – The synthesis of 5-amino-, 5-*N*-alkylamino-, and 5-*N*,*N*-dialkylamino-3-perfluoroheptyl-1,2,4-oxadiazoles has been realized with very good yields by ammonolysis or aminolysis of the 3-perfluoroheptyl-5-trichloromethyl-1,2,4-oxadiazole with ammonia, primary or secondary aliphatic amine. Some comments on the absorption spectra of fluorinated aminooxadiazoles are reported.

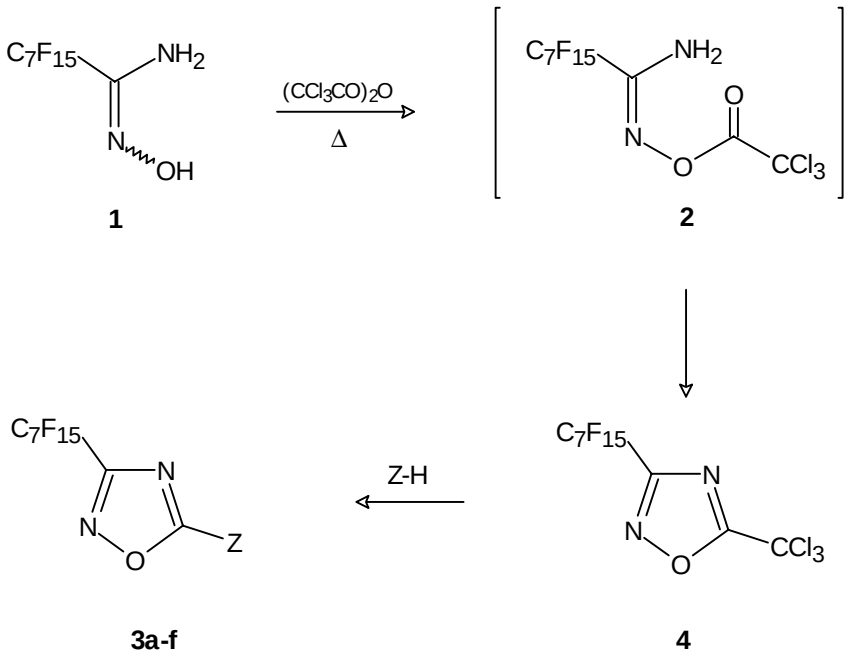
Fluorinated heterocycles are interesting compounds which are widely used in pharmaceuticals, agrochemicals and new materials.[1,2] As a consequence, their synthesis represents an interesting and well promising research area. In this respect, the synthesis of targeted fluorinated heterocyclic compounds generally considers heterocyclization reactions of fluorinated open-chain precursors or modifications of functional groups, rather than the direct introduction of fluorine or a fluorinated group into heterocyclic structure. [1,2] Among the building-block strategies, we recently experienced photochemical approaches exploiting photoinduced rearrangements of O-N containing azoles.[3] This procedure allowed us to synthesize fluorinated 1,2,4-oxadiazoles functionalized at C(3) of the ring by an amino or *N*-substituted amino group.[4,5] These results appear of some significance also because variously functionalised 1,2,4-oxadiazoles have been applied in pharmaceutical industry.[6]

RESULTS AND DISCUSSION

In the course of our studies dealing with synthetic methodologies for fluorinated oxadiazoles and their spectroscopic and photochemical properties, we became interested in realizing an efficient synthesis of 5-amino- (or 5-*N*-substituted amino-)-3-perfluoroalkyl-1,2,4-oxadiazoles. Taking into account that 5-

amino-1,2,4-oxadiazoles are generally obtained through nucleophilic displacement of a 5-chloro or a 5-trichloromethyl group with nitrogen nucleophiles,[7,8,9] to realize our pourpose we considered the ammonolysis or aminolysis of a C(5)-trichloromethyl substituted oxadiazole, confiding on its easy preparation by adopting the literature methodology.[7]

Thus, by reacting the easily accessible fluorinated amidoxime (**1**)[10] with trichloroacetic anhydride/trichloroacetic acid by melting at 120°C we directly obtained the 5-trichloromethyl-3-perfluoroheptyloxadiazole (**4**), clearly arising through the unisolated O-acylamidoxime (**2**). Subsequent reaction of compound (**4**) with methanolic ammonia, primary or secondary aliphatic amines in methanol at room temperature gave the desired compounds (**3a-f**) in almost quantitative yields (Scheme 1).[11] Physical and analytical data are reported in Table 1.



1 **2** **3a-f** **4**

Z-H = NH_3, $MeNH_2$, $NHMe_2$, CH_2=CH-CH_2NH_2, pyrrolidine, morpholine

3 **a**: Z = NH_2 **d**: Z = $NHCH_2CH=CH_2$

b: Z = NHMe **e**: Z = $N(CH_2)_4$

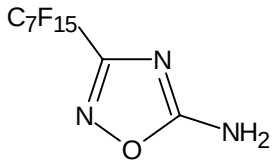
c: Z = NMe_2 **f:** Z = $N(CH_2)_2(CH_2)_2O$

Scheme 1

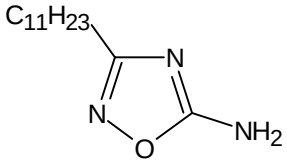
Table 1. Physical and analytical data for 5-aminooxadiazoles (**3a-f**).

Compd	Yield (%)	mp (°C)	IR(nujol) ν (cm^{-1})	^{1}H NMR (TMS), δ (ppm)	MS *m/z* (%)	Molecular Formula	Anal. Calcd/(Found) C	H	N
3a	95	83[a]	3340, 3280, 3210, 3180, 1665	8.71[b] (s)[c]	453 (M^+, 49), 134 (100), 69 (42)	$C_9H_2N_3OF_{15}$	23.86 (23.70)	0.44 (0.30)	9.27 (9.10)
3b	95	55[d]	3340, 3250, 3220, 3280, 1680	2.95[b] (m, 3H, Me), 8.98 (m, 1H, NH)[c]	467 (M^+, 100), 147 (31), 68 (25), 57 (39)	$C_{10}H_4N_3OF_{15}$	25.71 (25.60)	0.86 (0.80)	9.00 (8.90)
3c	90	oil	1650	3.21[e] (s)	481 (M^+, 100), 70 (34)	$C_{11}H_6N_3OF_{15}$	27.46 (27.30)	1.26 (1.10)	8.73 (8.50)
3d	90	49[d]	3320, 3230, 3200, 3100, 1670	3.96[b] (m, 2H, CH_2), 5.22 (m, 2H, CH_2), 5.89[e] (m, 1H, CH), 9.37 (br s, 1H, NH)[c]	493 (M^+, 74), 118 (22), 97 (20), 68 (100)	$C_{12}H_6N_3OF_{15}$	29.23 (29.10)	1.23 (1.20)	8.52 (8.40)
3e	80	oil	1650	2.08[e] (m, 4H), 3.63 (m, 4H)	507 (M^+, 100), 97 (9), 68 (25)	$C_{13}H_8N_3OF_{15}$	30.79 (30.60)	1.59 (1.40)	8.28 (8.10)
3f	95	51[d]	1670	3.70[e] (m, 4H), 3.82 (m, 4H)	523 (M+, 23), 479 (16), 145 (17), 118 (10), 55 (100)	$C_{13}H_8N_3O_2F_{15}$	29.84 (29.70)	1.54 (1.40)	8.03 (8.00)

[a] Crystallization solvent: benzene.
[b] in DMSO-d_6.
[c] exchangeable with D_2O.
[d] Crystallization solvent: light petroleum.
[e] in $CDCl_3$.



3a



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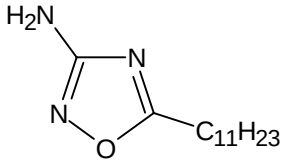

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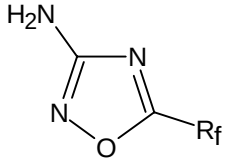

7a,b

a: $R_f = C_7F_{15}$
b: $R_f = C_3F_7$

Scheme 2

Although a detailed spectroscopic study on fluorinated oxadiazoles will follow, some comments on the absorption spectra of fluorinated aminooxadiazoles are due (See Table 2). The 5-amino- or 5-*N*-substituted amino compounds (**3a-f**) show λ_{max} values in the region of 229-242 nm. These values significantly differ from those of 3-amino-5-perfluoroalkyloxadiazoles isomers (**7a,b**)[4] that showed λ_{max} values at 259 and 257 nm, respectively. This difference can be explained if we consider the red-shift observed for fluorinated compounds (**7**) or (**3**) compared with the unfluorinated aminooxadiazoles (**5**)[12] and (**6**).[13] Taking into account that some 3-phenyl-5-perfluoroalkyl-1,2,4-oxadiazoles show λ_{max} value at 223 nm,[10] this shift should be ascribed to a synergic effect of the amino group and the highly electron-withdrawing perfluoroalkyl moiety. That is, on one hand, the perfluoroalkyl group lowers the LUMO, whereas the amino group is expected to raise the HOMO of the heterocycle. Clearly, this synergic effect of substituents is dependent to some extent on their mutual position in the oxadiazole ring: as expected on the basis of the electronic distribution of the 1,2,4-oxadiazole, this effect is greater for the 3-amino series containing the perfluoroalkyl group at C(5).

Table 2. UV spectra (in methanol) of aminooxadiazoles (**3**, **5**, **6**, **7)**.

Compound	λ_{max}	ε
3a	229	6000
3b	236	6700
3c	242	6500
3d	235	7800
3e	230	3700
3f	242	8100
5	215	8900
6	224	1700
7a	259	1200
7b	257	1200

EXPERIMENTAL

General: Melting points were determined on a Reichart-Thermovar hot-stage apparatus and are uncorrected. IR spectra (Nujol) were determined with a Perkin Elmer 257 instrument; UV spectra (methanol) were determined with a Jasco 7800 instrument; ^{1}H-NMR spectra were recorded on a Bruker AC 250 E spectrometer, and GC/MS determinations were carried out by using a VARIAN STAR 3400 CX/SATURN 2000 system or MICROMASS AUTOSPEC-ULTIMA electron beam energy 70 eV [for

compound (**4**)]. Flash chromatography was performed by using silica gel (Merck, 0.040-0.063 mesh) and mixtures of EtOAc and light petroleum (fraction boiling in the range 40-60°C) in varying ratios. Dry methanol (from Romil Pure Chemicals), methylamine and dimethylamine (33% in absolute ethanol, from Fluka), allylamine, pyrrolidine and morpholine (from Aldrich) were used as received. Freshly prepared saturated methanolic ammonia was used.
Compound (**1**) was prepared as reported.[7]

3-Perfluoroheptyl-5-trichloromethyl-1,2,4-oxadiazole (4). By adopting the reported procedure,[6] a mixture of perfluorooctanoylamidooxime (**1**) (5 g, 11.5 mmol), trichloroacetic acid (7.6 g, 46 mmol) and trichloroacetic anhydride (7.2 g, 23 mmol) was heated in an oil bath at 120°C for 90 min. The resulting solution was then cooled and diluted with water and ice and the aqueous layer removed. The oil residue was extracted with CCl_4, and the solution was washed with water, neutralized with aqueous (10%) $NaHCO_3$, and dried over Na_2SO_4. Removal of the solvent afforded the 3-perfluoroheptyl-5-trichloromethyl-1,2,4-oxadiazole (5.2 g, 80%). Compound (**4**)**,** oil, had *m/z* (rel. int.): 519 [M^+- Cl] (27), 394 (13), 366 (7), 131 (19), 69 (33) 44 (100). Anal. Calcd for $C_{10}N_2OCl_3F_{15}$. C, 21.62; N, 5.04. Found: C, 21.40; N, 4.90.

Synthesis of 5-aminooxadiazoles (3a-f). General procedure. To compound (**4**) (0.5 g, 0.9 mmol) in dry methanol (50 mL) the appropriate amine (9 mmol) was added and the mixture was left at rt for 6 h. After removal of the solvent under reduced pressure, the residue was treated with light petroleum and filtered giving compounds (**3a**) (95%), (**3b**) (95%), (**3d**) (90%), and (**3f**) (95%). In the case of the reaction with dimethylamine and pyrrolidine the residue was chromatographed yielding **3c** (90%) and **3e** (80%), respectively.
Analytical and physical data are reported in Table 1.

ACKNOWLEDGEMENT

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