An *ANRORC* approach to the synthesis of perfluoroalkylated 1,2,4-triazole-carboxamides

Antonio Palumbo Piccionello,* Andrea Pace, Silvestre Buscemi, and Nicolò Vivona

Dipartimento di Chimica Organica "E. Paternò", Università degli Studi di Palermo, Viale delle Scienze - Parco d'Orleans II, I-90128 Palermo, Italy.
E-mail: apalumbo@unipa.it

Dedicated to Prof. Henk C. van der Plas on his 80th birthday

Abstract

A series of perfluoroalkyl-1,2,4-triazole-carboxamides has been obtained through an *ANRORC-like* rearrangement (*A*ddition of *N*ucleophile, *R*ing-*O*pening and *R*ing-*C*losure) of 5-perfluoroalkyl-1,2,4-oxadiazole-3-carboxamides with methylhydrazine or hydrazine. The initial addition of the bidentate nucleophile to the electrophilic C(5) of the 1,2,4-oxadiazole ring, followed by ring opening and ring closure, leads to the formation of triazoles in good yield under mild experimental conditions. In some cases, a competitive *ANRORC-enlargement* reaction to form 1,2,4-triazin-6-ones was also observed. Obtained carboxamidotriazoles have also been explored as precursors for the synthesis of 3(5)-perfluoroalkyl-1,2,4-triazoles

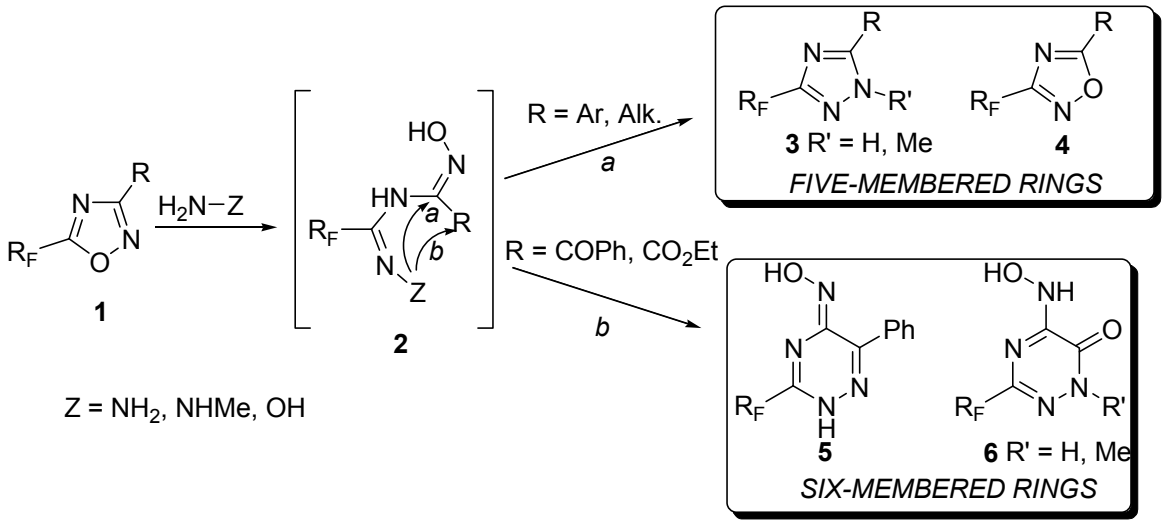
Keywords: Fluorinated heterocycles, triazole, oxadiazole, *ANRORC* rearrangements

Introduction

Synthesis of fluorinated heterocycles represents an interesting research field due to their unique properties. In particular, in the last years, fluorinated 1,2,4-triazoles have attracted much attention because of useful applications in many areas. In the field of material science they have been employed as room temperature ionic liquid,[1] liquid crystals[2] as well as ligands in blue emitting Iridium complex for OLED devices.[3] As pharmaceuticals they have been proposed as COX inhibitors,[4] as potent non-nucleoside inhibitors of the HIV-1 reverse transcriptase,[5] and Sitagliptin (*MK0431*), a trifluoromethylated 1,2,4-triazole derivative, is employed in the treatment of type II diabetes.[6] Moreover, fluorinated 1,2,4-triazole salts have been employed as catalysts in the Stetter reaction.[7] On the other hand, 1,2,4-triazole-carboxamides have emerged as an important class of antiviral compounds. For instance, Ribavirin, a triazole-carboxamide nucleoside, was the first synthetic nucleoside showing antiviral activity against several viruses.[8]

To date, it is still the only low molecular-weight drug available for treating viral infections caused by hepatitis C virus (HCV),[9] although some other triazole-carboxamide derivatives have been proposed for the treatment of HCV,[10] and showed activity against the tobacco mosaic virus.[11] Finally, 1,2,4-triazole-carboxamide have been recently exploited as structural motifs in the field of pseudo-peptide engineering.[12] In the frame of our research on fluorinated heterocycles, we have recently used the *ANRORC* approach as a valuable method for the obtainment of several fluorinated heterocyclic targets.[13] *ANRORC* processes (consisting of an initial *A*ttack of *N*ucleophile followed by *R*ing-*O*pening and *R*ing-*C*losure) have been extensively studied by Van der Plas and his coworkers[14] and represent an useful tool, in the hand of the synthetic heterocyclic chemist, to achieve the ring transformation of heterocyclic systems.
In this context, we have recently investigated the reactivity of 5-perfluoroalkyl-1,2,4-oxadiazoles **1** with bidentate nucleophiles such as hydrazine, methylhydrazine or hydroxylamine, and reported their *ANRORC-like* rearrangements into triazoles **3**,[13a,b,f] 1,2,4-oxadiazole regioisomers **4**,[13e] and 1,2,4-triazines **5**,**6**.[13a,d]

From a mechanistic point of view, 1,2,4-oxadiazole **1** reacted as a 1,3-dielectrophilic reagent; in fact, the presence of a strongly electronwithdrawing perfluorinated chain makes the C(5) (of the azole ring) a good electrophilic site, and allows the initial nucleophilic attack and ring-opening steps. In the subsequent steps, the cyclization can lead to different rings, depending on the nature of electrophilic sites present on the open-chain intermediate **2** (Scheme 1). Moreover, considering the regiochemical issue related to the use of asymmetric dinucleophiles, attack of the $-NH_2$ moiety to the C(5) of the oxadiazole was preferentially observed in all the studied cases.

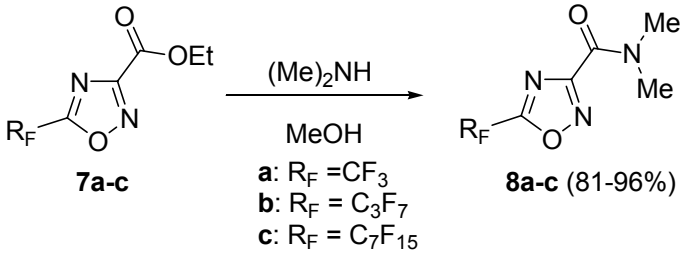


Scheme 1

On the basis of this general reactivity, we have considered the use of the *ANRORC* approach for the synthesis of fluorinated 1,2,4-triazole-carboxamides, by using 3-carboxamido-5-perfluoroalkyl-1,2,4-oxadiazoles. Considering the low electrophilic character of the carboxamido moiety, selected fluorinated 1,2,4-oxadiazoles could in fact act as potential 1,3-dielectrophiles in the reaction with hydrazines, becoming valid synthons for the obtainement of perfluoroalkyl-carboxamido-1,2,4-triazole.

Results and Discussion

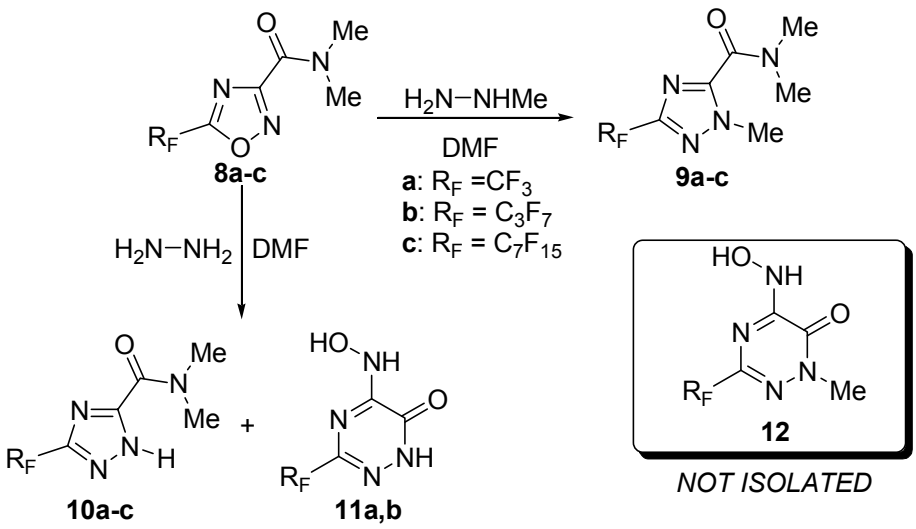
Starting 5-perfluoroalkyl-1,2,4-oxadiazole-3-carboxamides **8a-c** were obtained from the corresponding esters **7**,[13a] by reaction with dimethylamine in MeOH at room temperature (Scheme 2).



7a-c **8a-c** (81-96%)

Scheme 2

The obtained 1,2,4-oxadiazoles **8** were reacted in DMF at room temperature with the chosen hydrazine reagent. Unfortunately, the reaction with phenylhydrazine produced a complex mixture of products and was not considered of synthetic utility. On the other hand, when methylhydrazine was employed as nucleophile, 1-methyl-3-perfluoroalkyl-1,2,4-triazole-5-carboxamide **9a-c** were obtained in good yield (Scheme 3, Table 1). On the other hand, by using hydrazine as nucleophile, besides the expected fluorinated 1,2,4-triazoles **10a-c**, formation of 1,2,4-triazinones **11**[13a] was observed in some cases (Scheme 3, Table 1). The structures of fluorinated triazoles **9** and **10** were confirmed by analytical and spectroscopic data (^{1}H NMR, IR and GC-MS), while triazinones **11a,b** were identified by comparison with authentic sample obtained from *ANRORC* rearrangement of the corresponding esters **7a,b** with hydrazine.[13a]



Scheme 3

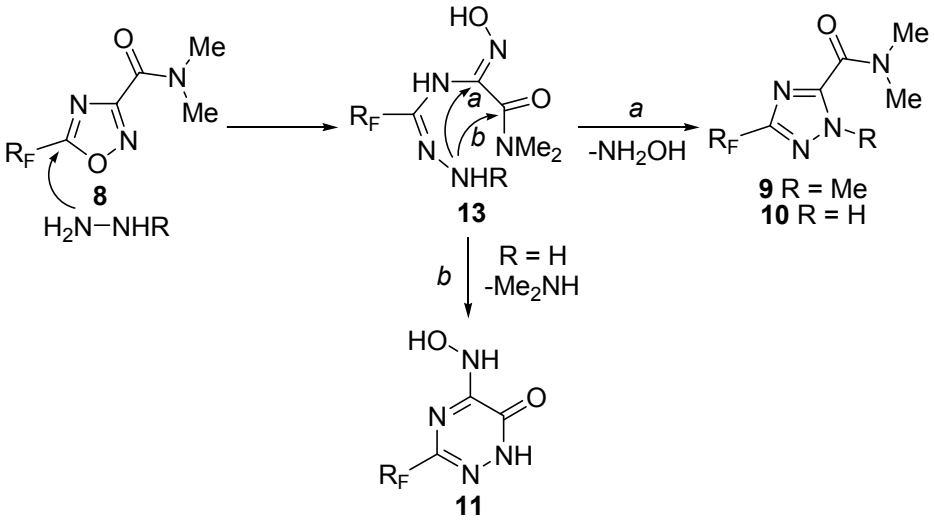
Table 1. Products distribution for hydrazinolysis reactions of oxadiazoles **8**

Substrate	R_F	Nucleophile	Triazole	Triazine
8a	CF_3	NH_2NHMe	**9a** (53%)	-
8b	C_3F_7		**9b** (65%)	-
8c	C_7F_{15}		**9c** (81%)	-
8a	CF_3	NH_2NH_2	**10a** (31%)	**11a** (27%)
8b	C_3F_7		**10b** (54%)	**11b** (17%)
8c	C_7F_{15}		**10c** (92%)	-

The regiochemistry of methyl-1,2,4-triazoles **9** was assigned by means of HMBC experiments. Representatively, the ^{1}H-^{13}C HMBC spectrum of **9c** revealed the presence of a long-range coupling between the methyl signal at 4.16 ppm and the quaternary carbon at 149.0 ppm. On the other hand, the long-range coupling has not been observed between the methyl hydrogens and the quaternary C(3) carbon at 151.1 ppm, easily recognizable as a triplet because of geminal C-F coupling ($^{2}J_{C\text{-}F}$ = 28.6 Hz) with the CF_2 moiety. Finally, long-range coupling between the two methyl signal of dimethylamino moiety (3.14 and 3.32 ppm) and remaining quaternary carbon at 157.9 ppm, allows the identification of the latter as the carboxamido carbon.

Interestingly, with methylhydrazine, formation of fluorinated methyl-triazinones **12** was not observed (see Scheme 3). The absence of these compounds from reaction mixtures was determined by using authentic samples of **12** as reference.[13a]

From a mechanistic point of view, formation of the obtained compounds could be explained on the basis of two competitive *ANRORC-like* rearrangements (Scheme 4).



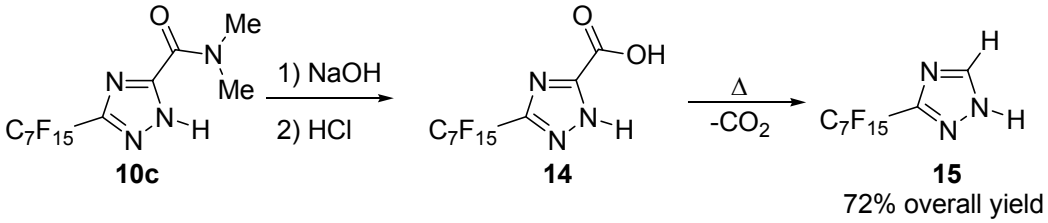
Scheme 4

Both pathways starts with the initial attack of -NH_2 end of nucleophile to the C(5) of the 1,2,4-oxadiazole ring, activated by the perfluoroalkyl moiety. The obtained open-chain intermediate **13** could then cyclize following two pathways: *i)* attack of the β-nitrogen of the nucleophile at the former C(3) of the oxadiazole ring to form triazoles **9** and **10**, with elimination of one molecule of hydroxylamine (*path a*);[13b,e,f] *ii)* attack of the β-nitrogen of the nucleophile to the side-chain electrophilic site (carboxamide) to form 1,2,4-triazines **11** with elimination of one molecule of dimethylamine (*path b*).[13a,d]

In our opinion, when the reaction is performed with methylhydrazine, *path b* results suppressed probably due to steric hindrance between the –NHMe and dimethylamino groups,

which inhibits the cyclization step. On the other hand, in the reaction with hydrazine, the two paths became competitive and the **10**:**11** product ratio is affected by the length of the perfluoroalkyl chain. In fact, triazole yield increase with carbon number of the R_F chain, while, at the same time, a decrease in triazine yield is observed. These data suggest that the fluoroalkyl moiety size has a role in determining the regioselectivity during the cyclization step of intermediate **13**.

Finally, we have also considered the use of carboxamidotriazoles **10** as precursor of 3(5)-perfluoroalkyl-1,2,4-triazoles. Representative triazole **10c** was hydrolyzed under basic conditions to give quantitatively the corresponding triazolecarboxylic acid **14**, which was decarboxylated under solvent-free conditions to the corresponding 3(5)-perfluoroalkyl-1,2,4-triazole **15** (Scheme 5).



Scheme 5

Conclusions

In conclusion, an *ANRORC* approach for the synthesis of various fluorinated 1,2,4-triazole-carboxamides has been developed. In its turn, obtained triazole-carboxamide has been used as precursors for the synthesis of mono-substituted perfluoroalkyl-1,2,4-triazoles.

Experimental Section

General Procedures. Melting points were determined on a Reichart-Thermovar hot-stage apparatus and are uncorrected. IR spectra (Nujol) were determined with a Shimadzu FTIR-8300 instrument; ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER 300 Avance spectrometer with TMS as an internal standard. GC–MS determinations were carried out on a VARIAN STAR 3400 CX/SATURN 2000 system. Flash chromatography was performed by using silica gel (Merck, 0.040–0.063 mm) and mixtures of ethyl acetate and petroleum ether (fraction boiling in the range of 40–60 °C) in various ratios. Compounds **7a-c**[13a] were obtained as previously reported.

Reaction of 1,2,4-oxadiazoles 7 with dimethylamine. General procedure

To a mixture of oxadiazole **7** (1 mmol) in MeOH (20 mL), an excess of dimethylamine (1.1 eq.) was added. After stirring for 3h at rt the solvent was eliminated. Chromatography of the residue gave 3-*N,N*-dimethylcarboxamido-5-perfluoroalkyl-1,2,4-oxadiazoles **8**.

3-*N,N*-Dimethylcarboxamido-5-trifluoromethyl-1,2,4-oxadiazole (8a). 81% Yield; yellow oil; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ 3.12 (s, 3H), 3.14 (s, 3H); FT-IR (Nujol) 1672 cm^{-1}. GC-MS (*m/z*): 209 (100%); Anal. Calcd. for $C_6H_6F_3N_3O_2$: C, 34.46; H, 2.89; N, 20.09. Found: C, 34.50; H, 2.70; N, 20.20.

3-*N,N*-Dimethylcarboxamido-5-heptafluoropropyl-1,2,4-oxadiazole (8b). 87% Yield; yellow oil; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ 3.14 (s, 3H), 3.17 (s, 3H); FT-IR (Nujol) 1664 cm^{-1}. GC-MS (*m/z*): 309 (100%); Anal. Calcd. for $C_8H_6F_7N_3O_2$: C, 31.08; H, 1.96; N, 13.59. Found: C, 31.20; H, 2.00; N, 13.40.

3-*N,N*-Dimethylcarboxamido-5-pentadecafluoroheptyl-1,2,4-oxadiazole (8c). 96% Yield; mp 55-57°C (white crystals from petroleum ether); ^{1}H NMR (300 MHz, *CDCl$_3$*) δ 3.13 (s, 3H), 3.18 (s, 3H); FT-IR (Nujol) 1677 cm^{-1}. GC-MS (*m/z*): 509 (100%); Anal. Calcd. for $C_{12}H_6F_{15}N_3O_2$: C, 28.31; H, 1.19; N, 8.25. Found: C, 28.30; H, 1.10; N, 8.30.

Hydrazinolysis reactions of 1,2,4-oxadiazoles 8 in DMF. General procedure

To a mixture of oxadiazole **7** (1 mmol) in DMF (3 mL), an excess of methylhydrazine or hydrazine (3 eq.) was added. After stirring for 3h at rt the mixture was diluted with 1 M HCl (50 mL) and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated. The residue was then chromatographed.

Reaction of oxadiazole 8a with methylhydrazine

1-Methyl-5-*N,N*-dimethylcarboxamide-3-trifluoromethyl-1,2,4-triazole (9a). 53% Yield; mp 44-47°C (white crystals from petroleum ether); ^{1}H NMR (300 MHz, *CDCl$_3$*) δ 3.13 (s, 3H), 3.32 (s, 3H), 4.16 (s, 3H); ^{13}C NMR (75 MHz, *CDCl$_3$*) δ 36.1 (Me), 38.7 (Me), 39.1 (Me), 117.3 (q, $^1J_{C\text{-}F}$ = 268.5 Hz, CF_3), 148.8 (Cq, C-5), 151.7 (q, $^2J_{C\text{-}F}$ = 39.7 Hz, C-3), 158.0 (Cq, C(O)N); FT-IR (Nujol) 1653 cm^{-1}. GC-MS (*m/z*): 222 (100%); Anal. Calcd. for $C_7H_9F_3N_4O$: C, 37.84; H, 4.08; N, 25.22. Found: C, 37.90; H, 4.10; N, 25.10.

Reaction of oxadiazole 8b with methylhydrazine

1-Methyl-5-*N,N*-dimethylcarboxamide-3-heptafluoropropyl-1,2,4-triazole (9b). 65% Yield; viscous yellow oil; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ 3.16 (s, 3H), 3.34 (s, 3H), 4.18 (s, 3H); ^{13}C NMR (75 MHz, *CDCl$_3$*) δ 35.9 (Me), 38.6 (Me), 38.8 (Me), 108.5 (tq, $^1J_{C\text{-}F}$=264.7, $^2J_{C\text{-}F}$=37.9 Hz, CF_2), 110.8 (tt, $^1J_{C\text{-}F}$=253.7, $^2J_{C\text{-}F}$=31.2 Hz, CF_2), 117.8 (qt, $^1J_{C\text{-}F}$ = 286.7 Hz, $^2J_{C\text{-}F}$ = 33.4 Hz, CF_3), 149.0 (Cq, C-5), 150.8 (t, $^2J_{C\text{-}F}$ = 28.5 Hz, C-3), 157.9 (Cq, C(O)N); FT-IR (Nujol) 1648 cm^{-1}. GC-MS (*m/z*): 322 (100%); Anal. Calcd. for $C_9H_9F_7N_4O$: C, 33.55; H, 2.82; N, 17.39. Found: C, 33.70; H, 2.70; N, 17.40.

Reaction of oxadiazole 8c with methylhydrazine

1-Methyl-5-*N,N*-dimethylcarboxamide-3-pentadecafluoroheptyl-1,2,4-triazole (9c). 81% Yield; viscous yellow oil; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ 3.14 (s, 3H), 3.32 (s, 3H), 4.16 (s, 3H); ^{13}C NMR (75 MHz, *CDCl$_3$*) δ 34.7 (Me), 38.7 (Me), 39.2 (Me), 106.8-115.5 (m, overlapped CF_2 signals), 117.3 (qt, $^1J_{C\text{-}F}$ = 286.7 Hz, $^2J_{C\text{-}F}$ = 33.1 Hz, CF_3), 149.0 (Cq, C-5), 151.1 (t, $^2J_{C\text{-}F}$ = 28.6 Hz, C-3), 157.9 (Cq, C(O)N); FT-IR (Nujol) 1654 cm^{-1}. GC-MS (*m/z*): 522 (100%); Anal. Calcd. for $C_{13}H_9F_{15}N_4O$: C, 29.90; H, 1.74; N, 10.73. Found: C, 29.80; H, 1.80; N, 10.70.

Reaction of oxadiazole 8a with hydrazine

Chromatography of the residue gave **10a** (31% yield) and **11a**[13a] (27% yield).

5-*N,N*-Dimethylcarboxamide-3-trifluoromethyl-1*H*-1,2,4-triazole (10). Mp 137-139°C (yellowish crystals from petroleum ether); ^{1}H NMR (300 MHz, DMSO-*d$_6$*) δ 3.11 (s, 3H), 3.44 (s, 3H), 15.81 (s, 1H, exch. with D_2O); ^{13}C NMR (75 MHz, *CDCl$_3$*) δ 37.4 (Me), 39.1 (Me), 119.1 (q, $^1J_{C\text{-}F}$ = 268.4 Hz, CF_3), 150.8 (Cq, C-5), 154.2 (q, $^2J_{C\text{-}F}$ = 39.7 Hz, C-3), 157.3 (Cq, C(O)N); FT-IR (Nujol) 3122, 1653 cm^{-1}. GC-MS (*m/z*): 208 (100%); Anal. Calcd. for $C_6H_7F_3N_4O$: C, 34.62; H, 3.39; N, 26.92. Found: C, 34.70; H, 3.50; N, 26.70.

Reaction of oxadiazole 8b with hydrazine

Chromatography of the residue gave **10b** (54% yield) and **11b**[13a] (17% yield).

5-*N,N*-Dimethylcarboxamide-3-heptafluoropropyl-1*H*-1,2,4-triazole (10b). Mp 132-135°C (white crystals from petroleum ether); ^{1}H NMR (300 MHz, DMSO-*d$_6$*) δ 3.11 (s, 3H), 3.42 (s, 3H), 15.96 (s, 1H, exch. with D_2O); ^{13}C NMR (75 MHz, *CDCl$_3$*) δ 37.4 (Me), 39.1 (Me), 106.8-119.8 (m, overlapped signals), 151.0 (Cq, C-5), 153.5 (t, $^2J_{C\text{-}F}$ = 27.8 Hz,C-3), 157.3 (Cq, C(O)N); FT-IR (Nujol) 3113, 1636 cm^{-1}. GC-MS (*m/z*): 308 (100%); Anal. Calcd. for $C_8H_7F_7N_4O$: C, 31.18; H, 2.29; N, 18.18. Found: C, 31.10; H, 2.20; N, 18.30.

Reaction of oxadiazole 8c with hydrazine

5-*N,N*-Dimethylcarboxamide-3-pentadecafluoroheptyl-1*H*-1,2,4-triazole (10c). 92% Yield; mp 127-130°C (white crystals from petroleum ether); ^{1}H NMR (300 MHz, DMSO-*d$_6$*) δ 3.16 (s, 3H), 3.44 (s, 3H), 15.92 (s, 1H, exch. with D_2O); ^{13}C NMR (75 MHz, *CDCl$_3$*) δ 37.4 (Me), 39.0 (Me), 106.8-120.0 (m, overlapped signals), 151.0 (Cq, C-5), 153.7 (bs, C-3), 157.1 (Cq, C(O)N); FT-IR (Nujol) 3125, 1636 cm^{-1}. GC-MS (*m/z*): 508 (100%); Anal. Calcd. for $C_{12}H_7F_{15}N_4O$: C, 28.36; H, 1.39; N, 11.02. Found: C, 28.40; H, 1.40; N, 11.00.

Hydrolysis of triazole-carboxamide (10c)

10c (1 mmol) was suspended in NaOH 2M (30 mL) and refluxed for 24h. After cooling, the solution was acidified with HCl 1M until complete precipitation of a white solid which was filtered giving **5-pentadecafluoroheptyl-1*H*-1,2,4-triazole-3-carboxylic acid 14** quantitatively.

14: mp 100-101°C (white crystals from water); FT-IR (Nujol) 3210, 3120, 3055, 1709 cm^{-1}. GC-MS (*m/z*): 481 (100%); Anal. Calcd. for $C_{10}H_2F_{15}N_3O_2$: C, 24.96; H, 0.42; N, 8.73. Found: C, 24.90; H, 0.20; N, 8.40.

Decarboxylation of triazole-3-carboxylic acid (14)

Carboxylic acid **14** was placed in a sealed tube and heated at 110°C for 5h. Chromatography of the residue gave **3(5)-pentadecafluoroheptyl-1,2,4-triazole 15**: 72% yield; mp 122-123°C (white crystals from water); ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H); FT-IR (Nujol) 3106 cm^{-1}. GC-MS (*m/z*): 437 (100%); Anal. Calcd. for $C_9H_2F_{15}N_3$: C, 24.73; H, 0.46; N, 9.61. Found: C, 24.90; H, 0.40; N, 9.70.

Acknowledgements

Financial support through the Italian MIUR and University of Palermo is gratefully acknowledged.

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