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Synthesis of fluorinated 1,2,4-oxadiazin-6-ones through ANRORC rearrangement of 1,2,4-oxadiazoles

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ABSTRACT

The reaction of 3-ethoxycarbonyl-5-perfluoroalkyl-1,2,4-oxadiazoles with hydroxylamines has been investigated, evidencing the possibility of competitive reaction paths. Nucleophilic addition of hydroxylamine to the electrophilic C(5) of the 1,2,4-oxadiazole ring, followed by ring-opening and ring-closure with enlargement, leads to high yield and in very mild experimental conditions to the formation of 5-hydroxyamino-3-perfluoroalkyl-6*H*-1,2,4-oxadiazin-6-ones, one of these presenting water gelation ability. In turn, reactions with *N*-methylhydroxylamine lead the exclusive formation of 4-perfluoroacylamino-2-methyl-2*H*-1,2,5-oxadiazol-3-ones through the well known Boulton–Katritzky rearrangement.

In the field of heterocyclic chemistry, ring-rearrangement reactions represent an important tool for the obtainment of structures that are otherwise difficult to synthesize.[1] In this context, *ANRORC* rearrangements, namely consisting of an initial *A*ttack of the *N*ucleophile followed by *R*ing-*O*pening and *R*ing-*C*losure, provide an useful synthetic approach in the azine series, as extensively reported by Van der Plas and his coworkers.[2] On the other hand, *ANRORC-like* reactivity of five-membered heterocycles is restricted to few examples, consisting of highly activated ring systems.[3]

In the frame of our ongoing studies on fluorinated azoles, we have recently reported some examples of *ANRORC-like* reactivity of fluorinated 1,2,4-oxadiazoles with 1,2-bidentate nucleophiles such as hydrazine, methylhydrazine and hydroxylamine, configuring fluorinated oxadiazoles as versatile synthons for the formation, in high yield and under mild conditions, of fluorinated heterocycles such as 1,2,4-triazoles,[4] 1,2,4-oxadiazoles,[5] 1,2,4-triazines,[6] 1,2,4-triazin-6-ones[4b] and indazoles[7] (Scheme 1).

The reported reactivity is consistent with the behaviour of the 1,2,4-oxadiazole ring as an 1,3- or 1,4-dielectrophile, initially reacting at C(5) position, activated by the fluorinated moiety. In this report we have investigated the reactivity of 3-ethoxycarbonyl-5-perfluoroalkyl-1,2,4-oxadiazoles **7**,[4b] as 1,4-dielectrophiles, in the presence of hydroxylamine and *N*-methylhydroxylamine, as 1,2-dinucleophile, with the aim of obtaining fluorinated derivatives of 1,2,4-oxadiazinones. 1,2,4-Oxadiazinones have been previously reported as 6-oxa analogues of pyrimidine nucleosides,[8] and show antimicrobial activity.[9] To the best of our knowledge, no fluorinated 1,2,4-oxadiazinones have been previously reported.

Starting oxadiazoles **7a–c** were prepared, through the conventional amidoxime route, accordingly to our previous report.[4b] Compounds **7a–c** were allowed to react in DMF at rt with an excess of hydroxylamine or *N*-methylhydroxylamine free bases, generated in situ from the corresponding hydrochloride and a stoichiometric amount of *t*-BuOK.[10]

Reaction with hydroxylamine allows direct obtainment of 5-hydroxyamino-3-perfluoroalkyl-6*H*-1,2,4-oxadiazin-6-ones **8a–c**[11] (77–98% yield) (Scheme 2). When *N*-methylhydroxylamine was employed as nucleophile, a substantial change in reactivity was observed. In fact, fluorinated 1,2,4-oxadiazin-6-ones were not observed, and instead formation of the 2-methyl-4-perfluoroacylamino-2*H*-1,2,5-oxadiazol-3-ones **9**[12] was observed (Scheme 2). During chromatographic purification, hydrolysis of products **9** into 4-amino-2-methyl-2*H*-1,2,5-oxadiazol-3-one **10**[12] was always observed, particularly in the case of the trifluoroacetyl derivative which could not be isolated (Scheme 2).

The structures of the obtained products were assigned by means of analytical and spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, HRMS) and for representative compound **8a**, unambiguously confirmed by electrospray negative ion MS/MS measurements, carried out by linear ion trap-Orbitrap analyzers.[13] For compound **8a**, by selecting the species $[M-H]^-$ ($[C_4HN_3O_3F_3]^-$, *m/z* 195.9974 error = −0.91 ppm) as a precursor ion, the species $[(M-H)-OH]^-$, $[(M-H)-NO]^-$ and $[(M-H)-CO_2N]^-$ are formed. In addition, a key fragment ion due to $[C_2N_2F_3]^-$ (*m/z* 109.0018 error = −0.70 ppm) is detected (Fig. 1). This is attributable to the

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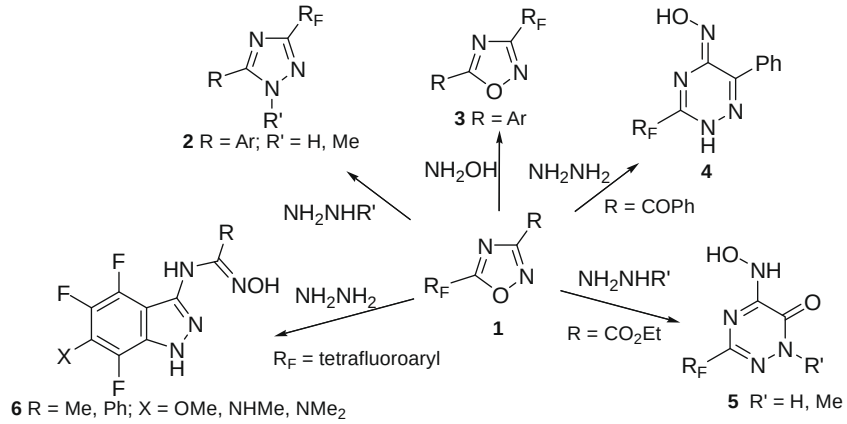
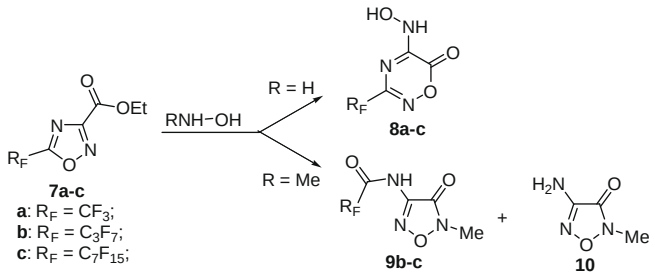


Scheme 1.



Scheme 2.

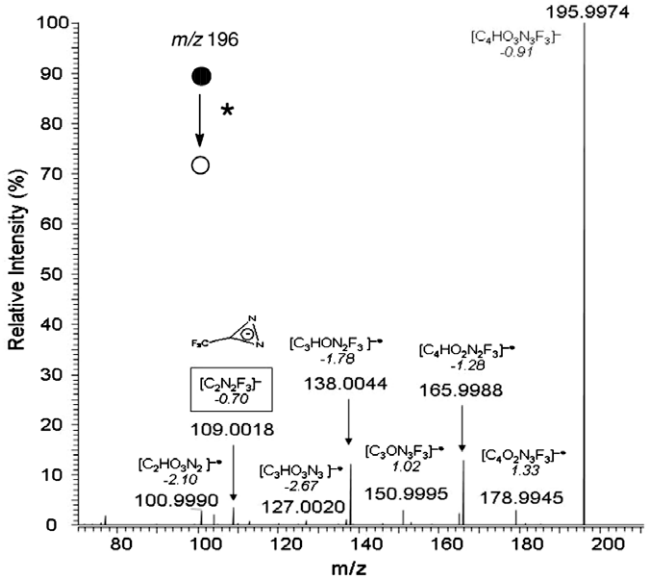


Figure 1. Electrospray negative ion MS/MS spectrum of compound **8a** obtained at 100,000 resolution. Elemental formulae and mass measurement errors (ppm) are also reported.

3-(trifluoromethyl)diazirin-1-ide anion and indicates that the carbon C(3), in addition to the trifluoromethyl moiety, is bound to two nitrogen atoms, thus confirming the 1,2,4-oxadiazin-6-one structure reported in Scheme 2.

Serendipitously, during purification steps of fluorinated oxadiazinone **8c** hydrogel formation was observed. Hydrogelation ability of **8c** was reproduced from water suspension (above 5 wt %) upon heating and sonication on cooling (Fig. 2), and the formed hydrogel is stable for more than one month. So far, among low-molecular weight (LMW) hydrogelators,[14] only two examples of fluorinated derivatives, both containing anionic polar head groups, are reported in the literature.[15] In this context, compound **8c**, which presents an uncommonly small polar head-group (i.e., the hydroxyamino moiety) if compared with common sugar-based fluorinated surfactants,[16] represents a new entry of fluorinated LMW hydrogelators.

Formation of compounds **8** could be explained on the basis of an *ANRORC-like* ring-enlargement (Scheme 3, route *a*), which involves initial attack of the nitrogen end of the nucleophile on the C(5) of the 1,2,4-oxadiazole ring, activated by the perfluoroalkyl chain. The so-obtained oxadiazoline **11** develops into the open-chain intermediate **12**, which then undergoes the final ring-closure into **8**, with EtOH acting as leaving group. Formation of furazan **9** could be ascribed to an initial attack of the methylated nitrogen of the nucleophile on the ethoxycarbonyl moiety, with formation of hydroxamic acid intermediate **13**, which accordingly to the well known Boulton–Katritzky rearrangement[1a,g] (*BKR*) gave final 1,2,5-oxadiazol-3-one **9** (Scheme 3, route *b*).

This dichotomic behaviour of 1,2,4-oxadiazoles **7** could be related to the different steric hindrance and nucleophilicity of nitrogen atoms on the hydroxylamine reagent. In fact, while the less

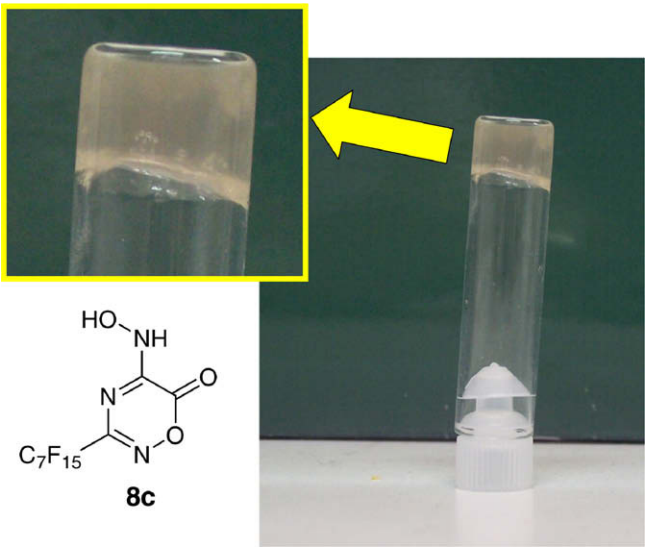
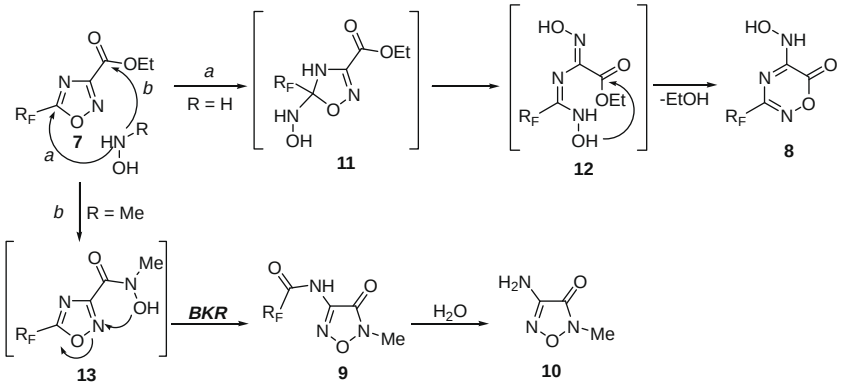


Figure 2. Hydrogel formed from water solution (5 wt %) of compound **8c**.



Scheme 3.

hindered NH_2 nitrogen of hydroxylamine reacts exclusively at C(5) of the oxadiazole ring, the NHMe nitrogen will react exclusively with the ester moiety.

In conclusion, the study of the reactivity of 5-perfluoroalkyl-3-ethoxycarbonyl-1,2,4-oxadiazoles **7** with hydroxylamines confirmed the synthetic utility of the *ANRORC* approach and the versatility of fluorinated 1,2,4-oxadiazoles as synthons for heterocyclic targets. Moreover, the hydrogelation ability observed for neutral compound **8c** opens the way to the study of similar compounds as fluorinated LMW hydrogelators.

Acknowledgements

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10. *General procedure for reaction of oxadiazoles **7a–c** with hydroxylamines in DMF*: To a solution of hydroxylamine hydrochloride or *N*-methylhydroxylamine hydrochloride (5 mmol) in dry DMF (3 mL), *t*-BuOK (5 mmol) was added. The mixture was allowed to stir at rt for 30′. Then oxadiazole **7** (1 mmol) was added and stirring continued for 3 h at rt. The reaction mixture was then diluted with water (50 mL), neutralized with HCl 1 M and extracted with EtOAc (6 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained residue was chromatographed.
11. *Reaction of* **7a** *with hydroxylamine*: Chromatography of the residue gave 5-hydroxylamino-3-trifluoromethyl-6*H*-1,2,4-oxadiazin-6-one **8a** (98%). Compound **8a** is a viscous oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ10.59 (br s, 1H, exch. with D_2O), 12.18 (br s, 1H, exch. with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6, ^{1}H decoupled) δ 117.1 (q, J_{C-F} = 320.0 Hz, CF_3), 149.2 (Cq), 160.7 (q, J_{C-F} = 45.1 Hz, Cq), 170.9 (Cq); FT-IR (Nujol) 3212, 1703 cm^{-1}. GC/MS (*m*/*z*): 197 (M$^+$, 48), 178 (14), 167 (19), 138 (15), 69 (100); HRMS calcd for $C_4H_2F_3N_3O_3$: 197.0048. Found: 197.0045.
Reaction of **7b** *with hydroxylamine*. Chromatography of the residue gave 5-hydroxylamino-3-heptafluoropropyl-6*H*-1,2,4-oxadiazin-6-one **8b** (96%). Compound **8b** had mp 89–91 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.22 (br s, 1H, exch. with D_2O), 12.35 (br s, 1H, exch. with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6, ^{1}H decoupled) δ 105–119 (m, overlapped signals), 149.3 (Cq), 160.4 (t, J_{C-F} = 33.7 Hz), 170.9 (Cq); FT-IR (Nujol) 3145, 1676 cm^{-1}. GC/MS (*m*/*z*): 297 (M$^+$, 82), 267 (16), 239 (20), 69 (100); HRMS calcd for $C_6H_2F_7N_3O_3$: 296.9984. Found: 296.9979.
Reaction of **7c** *with hydroxylamine*. Chromatography of the residue gave *5-Hydroxylamino-3-pentadecafluoroheptyl-6H-1,2,4-oxadiazin-6-one* **8c** (77%). **8c** had mp 111–113 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) d 10.23 (bs, 1H, exch. with D_2O), 12.47 (bs, 1H, exch. with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6, ^{1}H decoupled) d 105–120 (m, overlapped signals),149.1 (Cq), 160.7 (t, J_{C-F} = 28.6 Hz), 171.1 (Cq); FT-IR (Nujol) 3254, 3178, 1693 cm^{-1}. GC/MS (*m*/*z*): 497 (M$^+$, 42), 478 (3), 439 (13), 69 (100); HRMS Calcd. for $C_{10}H_2F_{15}N_3O_3$: 496.9857. Found: 496.9854.
12. *Reaction of* **7a** *with N-methylhydroxylamine*: Chromatography of the residue gave 4-amino-2-methyl-2*H*-1,2,5-oxadiazol-3-one **10** (58%). Compound **10** had mp 199 °C (dec., EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.56 (s, 3H), 6.45 (s, 2H, exch. with D_2O); FT-IR (Nujol) 3399, 3312, 3259, 3201, 3165, 1749, 1703 cm^{-1}. GC/MS (*m*/*z*): 115 (M$^+$, 72), 58 (100); HRMS calcd for $C_3H_5N_3O_2$: 115.0382. Found: 115.0381.
Reaction of **7b** *with N-methylhydroxylamine*: Chromatography of the residue gave 4-heptafluorobutanoylamino-2-methyl-2*H*-1,2,5-oxadiazol-3-one **9b** (53%) and **10** (41%). Compound **9b** had mp 132–134 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.68 (s, 3H); FT-IR (Nujol) 3399, 3312, 3259, 3201, 3165, 1749, 1703 cm^{-1}. GC/MS (*m*/*z*): 311 (M$^+$, 59), 169 (100), 69 (73), 58 (27); HRMS calcd for $C_7H_4F_7N_3O_3$: 311.0141. Found: 311.0138.
Reaction of **7c** *with N-methylhydroxylamine*. Chromatography of the residue gave *4-pentadecafluoroctanoylamino-2-methyl-2H-1,2,5-oxadiazol-3-one* **9c** (67%) and **10** (22%). **9c** had mp 131–132 °C (EtOH); ^{1}H NMR (300 MHz, *Acetone-*d_6) d 3.68 (s, 3H), 9.13 (b, 1H, exch. with D_2O); ^{13}C NMR (75 MHz, *Acetone-*d_6, ^{1}H decoupled) d 33.2, 105–120 (m, overlapped signals),147.9 (Cq), 152.8 (Cq), 156.9 (t, J_{C-F} = 30.1 Hz); FT-IR (Nujol) 3190, 3037, 1752, 1701 cm^{-1}. GC/MS (*m*/*z*): 511 (M$^+$, 50), 369 (9), 169 (50), 69 (100), 58 (27); HRMS Calcd. for $C_{11}H_4F_{15}N_3O_3$: 511.0013. Found: 511.0014.
13. Electrospray measurements have been carried out on compound **8a** by using a LTQ-XP-Orbitrap instrument (Thermo, Bremen, D). Operated conditions of the ESI source were as follows: spray voltage 4.5 kV; capillary temperature 200 °C; sheath gas (nitrogen) flow rate, ca. 0.75 L/min. Ultra pure helium was the collision gas. CID collision energy: 0.5–1.0 eV (laboratory frame). The Orbitrap analyzer was operating in the resolution range 60,000–100,000, and was calibrated using the manufacturer's calibration mixture. Mass accuracies <2 ppm were determined before and after each session of experiments. 30–50 Scans were recorded and averaged for accurate mass measurements. Working solutions were introduced into each mass spectrometer using a syringe pump at a flow rate of 5 μL/min.
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