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Fluorinated Heterocyclic Compounds − The First Example of an Irreversible Ring-Degenerate Rearrangement on Five-Membered Heterocycles by Attack of an External Bidentate Nucleophile

Silvestre Buscemi,[a] Andrea Pace,[a] Ivana Pibiri,[a] Nicolò Vivona,*[a] Camilla Zaira Lanza,[b] and Domenico Spinelli*[b]

Dedicated to Professor Carlo Dell'Erba in the occasion of his 70th birthday

Keywords: Heterocycles / Nucleophilic substitution / Rearrangements / Ring−ring interconversion

The reactions of 5-perfluoroalkyl-1,2,4-oxadiazoles **3** with hydroxylamine in DMF give the regioisomeric 3-perfluoroalkyl-1,2,4-oxadiazoles **4** in excellent yields. This process is the first example of ring-degenerate rearrangement (RDR) occurring on five-membered heterocycles by attack of an external bidentate nucleophile, which replaces two heteroatoms of the ring. We suggest that an ANRORC-like mechanism occurs in which the addition of the nucleophilic nitrogen atom (NH_2OH) on the C(5) atom of **3** is followed by ring opening and irreversible ring-degenerate closure by attack of the nucleophilic oxygen atom (=NOH) on the C(3) atom of the original ring, realizing an elegant and efficient synthesis of **4** by a C(3)–C(5) annular switch. Ab initio computations on the starting materials and final products, as well as on the proposed intermediates, support the mechanism and shed light on the features of the reaction.

Introduction

Fluorinated organic compounds represent an interesting class of compounds that continue to fascinate organic chemists because of their peculiar physical, chemical, and electronic properties and the variety of their applications.[1] Indeed, fluoro derivatives are largely used in the field of high-temperature-resistant materials[2,3] and of biomedical materials (e.g., some polyfluorinated heterocyclic compounds can be used as components of artificial bloods because they are effective oxygen carriers).[1j]

Within this framework, and considering the importance of several azoles in medicinal chemistry, we are interested in developing synthetic methods for targeted fluorinated compounds.[4−6]

To this end, we have considered *building block strategies* rather than the direct introduction of fluorine or fluorinated groups into the heterocycle,[1,7] by using ring-rearrangement reactions[8−10] that involve the transformation of an easily prepared fluorinated heterocycle into a new fluorinated structure that could otherwise be obtained only by difficult and tedious procedures.

In this context, we have reported the synthesis of 3-amino-5-(perfluoroalkyl or polyfluorophenyl)-1,2,4-oxadiazoles by irradiation of fluorinated 3-(acylamino)furazans in the presence of ammonia or aliphatic amines.[4a][4b] We have also examined ring-to-ring interconversions requiring addition of a nucleophile to the starting heterocycle, followed by ring-opening and ring-closure steps (an ANRORC-like pattern).[9] In this framework, we have exploited the reactivity of 5-perfluoroalkyl-1,2,4-oxadiazoles **1** with hydrazine and reported the synthesis of 5-perfluoroalkyl-1,2,4-triazoles **2** (Scheme 1).[5] In this process, hydrazine behaves as a bidentate nucleophile, initially attacking the C(5) atom of the 1,2,4-oxadiazole ring before heterocyclization of the open-chain intermediates occurs by attack of the β-nitrogen atom of the hydrazine onto the C(3) atom of the starting 1,2,4-oxadiazole followed by displacement of a molecule of hydroxylamine. In the final step, the higher thermodynamic stability (i.e., the larger aromaticity)[11−13] of the formed 1,2,4-triazole ring, with respect to the starting 1,2,4-oxadiazole, plays an important role. Thus, because of their low aromaticity (e.g., evaluated by Bird's indexes),[12] 1,2,4-oxadiazoles appear to be suitable substrates for ring-to-ring interconversion,[8f,14,15] as well as because of the observation that ring opening in 1,2,4-oxadiazoles can occur at either the O(1)−N(2) or O(1)−C(5) bonds.[16]

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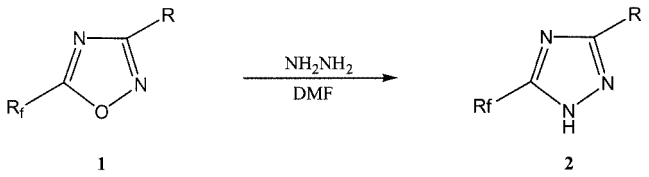


1 2

R = Ph; $C_{11}H_{23}$
R_f = CF_3; C_3F_7; C_7F_{15}

Scheme 1. Hydrazinolysis of 5-perfluoroalkyl-1,2,4-oxadiazoles

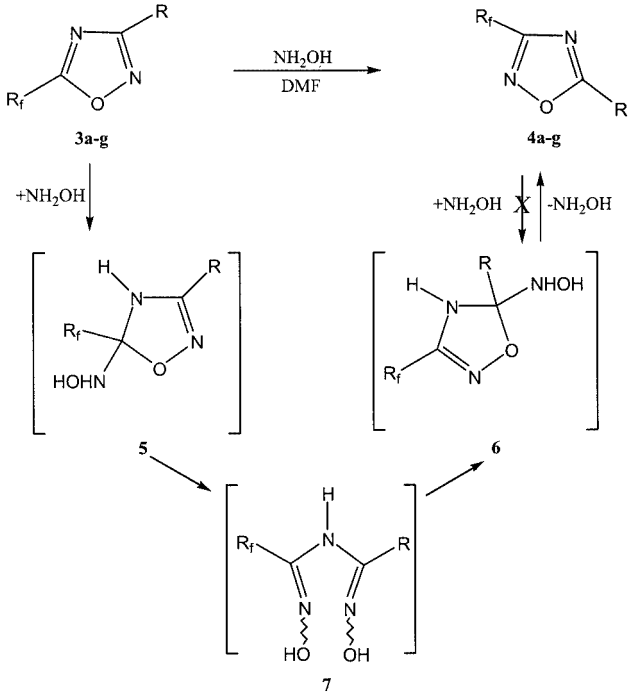
Interestingly, the use of the dipolar aprotic DMF as the reaction medium (by enhancing the nucleophilic character of the hydrazine and minimizing the occurrence of unfavorable solvolysis of the open-chain intermediates)[17] markedly improved the yield of the fluorinated 1,2,4-triazoles.

The results obtained using hydrazine as the reagent opened the way to a series of new ANRORC-type reactions on 1,2,4-oxadiazoles containing a perfluoroalkyl substituent at C(5). In this context, our interest was devoted to the identification of a reagent that is able to perform a ring-degenerate rearrangement (RDR) on the 1,2,4-oxadiazole moiety, thus realizing the first example of RDRs in five-membered ring derivatives by the action of an external bidentate nucleophile. As a matter of fact, Van der Plas and co-workers, who in the meantime were studying ANRORC reactions, discovered several examples of RDRs of six-membered heterocycles by attack of external nucleophiles, as well as by side-chain participation.[9] Examples of RDRs have been reported for five-membered heterocycles, too, but in most cases the reaction occurs as an intramolecular process by side-chain participation, and can be promoted thermally or photochemically, as well as by acids or bases. Specifically, when a three-atom side-chain participates, the resulting rearrangements represent a peculiar case of the Boulton–Katritzky reaction (BKR).[8b–8i,9,18–22] Cases of RDR involving external nucleophiles have been reported for five-membered heterocycles bearing a "good" leaving group.[9,23]

The appropriate reagent to realize an ANRORC-type RDR in the 1,2,4-oxadiazole series is hydroxylamine: a bidentate nucleophile that is able to attack with either its nitrogen or oxygen atom (thus replacing two heteroatoms of the ring), and whose reactivity seems to increase by the α-effect.[24] Moreover, this study was also stimulated by the fact that during the aforementioned hydrazinolysis we found some by-products whose formation is possibly linked to the action of the hydroxylamine formed during the reaction, which is able to compete with hydrazine in the nucleophilic process.[5]

Results and Discussion

The substrates selected for this study were 5-perfluoroalkyl-1,2,4-oxadiazoles **3a–g** (Scheme 2). All the reactions were carried out in DMF at room temperature and using hydroxylamine obtained in situ from the corresponding hydrochloride after reaction with potassium *tert*-butoxide. Thus, by using a very simple synthetic method, 1,2,4-oxadiazoles **3a–g** gave the 3-perfluoroalkyl-substituted regioisomers **4a–g**, which are otherwise difficult to obtain and/or unknown, in good to excellent yields (see Table 1). These results, which can be explained by assuming an ANRORC pattern, require a few appropriate comments. First of all, as already observed for hydrazinolysis, the occurrence of the reaction is determined by the presence and position of the perfluoroalkyl group, which makes the C(5) atom of the ring a rather electron-deficient site that is capable of being the site of the nucleophilic attack of hydroxylamine.



a: R = Ph; R_f = CF_3
b: R = Ph; R_f = C_3F_7
c: R = Ph; R_f = C_7F_{15}
d: R = *p*-$NO_2C_6H_4$; R_f = CF_3
e: R = *p*-$MeOC_6H_4$; R_f = CF_3
f: R = *p*-$MeOC_6H_4$; R_f = C_7F_{15}
g: R = $C_{11}H_{23}$; R_f = CF_3

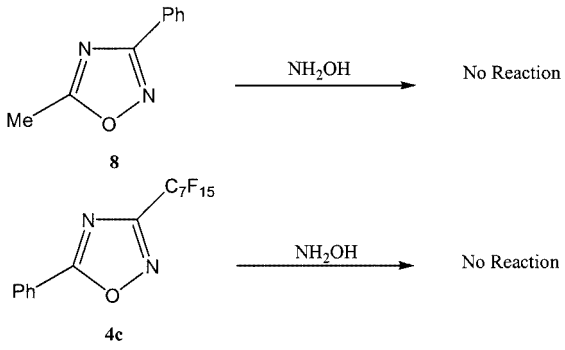
Scheme 2. Ring-degenerate rearrangements of oxadiazoles **3a–g** with hydroxylamine

Accordingly, neither the 5-methyl-3-phenyl- (**8**) nor the 3-perfluoroheptyl-5-phenyl-1,2,4-oxadiazole (**4c**; a regioisomer of **3c**) reacted with hydroxylamine under the experimental conditions outlined above (Scheme 3), which clearly indicates that the presence of the perfluoroalkyl group at C(5) is necessary for the occurrence of the nucleophilic attack and the subsequent ring-opening with cleavage of the C(5)–O(1) bond.

Interestingly, in the proposed mechanism, a molecule of hydroxylamine initially behaves as an N-nucleophile, attacking the C(5) atom of the 1,2,4-oxadiazole ring (with formation of **5**); later, however, when the open-chain intermediate

Table 1. Reaction of 5-perfluoroalkyl-1,2,4-oxadiazoles **3a**−**g** with hydroxylamine: synthesis of 3-perfluoroalkyl-1,2,4-oxadiazoles **4a**−**g**

R	R_f	Substrate	Product	Reaction time [h]	Yield [%]	Calculated ΔE [kJ·mol^{-1}]
Ph	CF_3	**3a**	**4a**	1.5	74	−17.8
Ph	C_3F_7	**3b**	**4b**	3	77	
Ph	C_7F_{15}	**3c**	**4c**	18	87	
p-$O_2NC_6H_4$	CF_3	**3d**	**4d**	1	94	−13.3
p-$MeOC_6H_4$	CF_3	**3e**	**4e**	4.5	82	−19.8
p-$MeOC_6H_4$	C_7F_{15}	**3f**	**4f**	144	70	
$C_{11}H_{23}$	CF_3	**3g**	**4g**	3.5	90	



Scheme 3. Failed ring-degenerate rearrangements

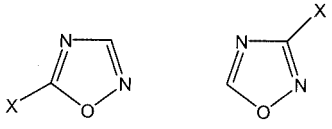
7 undergoes ring closure (with formation of **6**, also favored by base catalysis from the reaction medium) and re-aromatization (with formation of **4**), a molecule of hydroxylamine behaves as the leaving group. The observation that **3a** rearranges into **4a** also in the presence of a catalytic amount of hydroxylamine (NH_2OH/**3a** = 1:5) strongly supports our hypothesis.

As already pointed out by Boulton and Katritzky,[8g,8h] by us,[11] and by others,[8i] the driving force for ring-to-ring interconversions is thermodynamic in nature, giving the more stable product, and, thus, largely depends on the relative stability of the original and final rings. For ring-degenerate rearrangements, the original and final rings are the same, and so these reactions are often documented in the literature as being reversible processes with the overall equilibrium being more or less shifted towards one side.[9,18−22] In our case, therefore, the question arises as to why such a 1,2,4-oxadiazole-to-1,2,4-oxadiazole RDR interconversion is an irreversible process or, in other words, of how the substituents' positions affect the stability of the 1,2,4-oxadiazole derivatives.[25] The experimental results clearly point out that the presence of a strongly electron-withdrawing group is necessary and its position is strategically important for determining whether the reaction occurs or not, as well as the final equilibrium composition. The lack of reactivity of compound **8** is readily ascribed to a lack of electrophilicity of the annular carbon atoms of the oxadiazole ring, but the lack of reactivity of **4c** is clearly due to the peculiar position of the electron-withdrawing fluorinated substituent and confirms the irreversibility of the process.

A better and quantitative understanding of this reaction comes from the analysis of ab initio computational data regarding the thermodynamic stability of various substituted 1,2,4-oxadiazoles[26] as well as with regard to the geometry and charge distribution of the open-chain intermediates involved in the rearrangement of **3** onto **4**.

Theoretical Studies

Gas-phase ab initio computations were performed at the density functional theory (DFT) level on compounds **3a**,**d**,**e**, their regioisomers **4a**,**d**,**e**, some model compound **9a**−**g**, and their corresponding isomers **10a**−**g** (Scheme 4). All DFT molecular structures were fully optimized using the gradient method available in the GAUSSIAN98[27] program package and were rigorously characterized as minima according to the number of imaginary modes by applying a second-order derivative calculation. DFT-level geometry calculations were performed using the non-local hybrid Becke's three-parameter exchange functional, denoted as B3LYP,[28a] using the DZVP[28b] basis set, which is a local spin density (LSD) optimized basis set of double-ζ quality in the valence shell plus polarisation functions. The cheaper basis DZVP provides results very similar to those obtained with the more-extended basis 6-311+G*, as we have tested by calculating the structure of 1,2,4-oxadiazole and comparing it with structural data.[13c]



9a-g **10a-g**

a: X = NH_2 ΔE = 32.7 kJ mol^{-1}
b: X = OMe ΔE = 10.8 kJ mol^{-1}
c: X = Ph ΔE = 19.3 kJ mol^{-1}
d: X = Me ΔE = 8.6 kJ mol^{-1}
e: X = Cl ΔE = -1.0 kJ mol^{-1}
f: X = CF_3 ΔE = -3.7 kJ mol^{-1}
g: X = NO_2 ΔE = -8.9 kJ mol^{-1}

Scheme 4. Model compounds for calculating the effects of substituents on the stability of 1,2,4-oxadiazoles

We assume that the results calculated in the gas phase are similar to those in solution because of the similarity between the compounds **3** and **4** (i.e., we expect the same solvent effect for both of these compounds and, therefore, it should not affect their relative stability).

Further computational details, including Cartesians coordinates and computed total energies of optimized structures, are reported for **3a**,**d**,**e** and **4a**,**d**,**e** in Tables I−VI in the Supporting Information (see footnote on the first page of this article).

A first calculation on compounds **3a** and **4a** resulted in an unexpectedly significant $\Delta E = -17.8$ kJ·mol^{-1} (**4a** being more stable then **3a**, Table 1). Such a large difference (corresponding to a large reaction equilibrium constant, $K_{eq} > 10^3$, at room temp.) explains the absence of a mixture of the two regioisomers very well and guarantees the complete rearrangement of **3a** into **4a**. Similar results were obtained for the *p*-nitro- and *p*-methoxy-substituted pairs, **3d**/**4d** and **3e**/**4e** (Table 1), which, interestingly, have lower and higher ΔE values, respectively, relative to the unsubstituted pair.

Assuming similar steric requirements for each pair of regioisomers, we attribute the observed differences mostly to electronic effects; from the data in Table 1, it appears evident that the presence of the strongly electron-withdrawing trifluoromethyl group linked to C(5) in the 1,2,4-oxadiazole ring makes **3a** less stable than **4a**, which contains the same group linked at C(3). Of course, an opposite effect is exerted by an electron-donating substituent (relative to the oxadiazole ring), such as a phenyl group, linked to the C(5) or C(3) atoms, respectively. This hypothesis is strongly supported by those data in which the effects of different *para*-substituted phenyl substituents are compared; in fact, all things being equal (i.e., the position of the trifluoromethyl group), by increasing the electron-donating ability of the aryl substituent (on proceeding from phenyl to 4-methoxyphenyl) the value of ΔE increases; in contrast, upon decreasing the electron-donating ability of the aryl substituent (on proceeding from phenyl to 4-nitrophenyl), the value of ΔE decreases. These results strengthen the idea that the aryl substituent is coplanar with respect to the 1,2,4-oxadiazole ring, as supported by our ab initio calculations, in contrast with previous conclusions reached by others[26] on the basis of MNDO computations.

The hypotheses above are also confirmed by the data on the monosubstituted oxadiazoles **9** and **10** chosen as model compounds (Scheme 4). To differentiate the effects of electron-donating and -withdrawing substituents on the heterocycle's stability, we considered compounds **9a**−**g** and **10a**−**g**, i.e., monosubstituted 1,2,4-oxadiazoles, which bear at the C(5) and C(3) centers, respectively, substituents having very different electronic effects, ranging from the strongly electron-donating NH_2 and OMe groups (**a** and **b**), through C_6H_5, Me, and Cl groups (**c**, **d**, and **e**, having intermediate electronic requirements), to the strongly electron-withdrawing CF_3 and NO_2 groups (**f** and **g**).

Again, neglecting any possible steric factors and considering data referred to the gas phase (see above), we observed (see the complete data in Tables VII−XX of the Supporting Information) that when X is an electron-donating group the 5-substituted 1,2,4-oxadiazole is the more stable regioisomer (ΔE ranging from 8.0 to 32.7 kJ·mol^{-1}), whereas, when the substituent is electron-withdrawing the 3-substituted 1,2,4-oxadiazole is more stable (ΔE ranging from 3.7 to 8.9 kJ·mol^{-1}). 5-Chloro-1,2,4-oxadiazole (**9e**), as expected, has practically the same energy content of its regioisomer **10e** (i.e., **10e** is only a little more stable than **9e**, $\Delta E = 1.0$ kJ·mol^{-1}); this result can be explained by considering the somewhat compensating effects exerted by chlorine atoms.

Although we performed no complete kinetic study of the reaction, it is evident from the data in Table 1 that the substituent also affects the overall reaction rate. Actually, one can observe that the reaction times for **3a**, **3b**, and **3c** increase from 1.5 to 3 and 18 h, respectively. Considering that these compounds differ only in the lengths of their perfluoroalkyl chains, and, thus, they have very different steric requirements, this observation clearly indicates the occurrence of a primary kinetic steric effect.[29] This result is even more evident by comparing the data of **3e** and **3f**, for which the change of the perfluoroalkyl group from CF_3 to C_7F_{15} causes a > 30-fold increase of the reaction time.

Moreover, the rate of the heterocyclization step of **7** into **6** should be affected by electronic effects, which influence the electrophilic character of the C(3) atom (at which the ring-closure takes place) of the initial 1,2,4-oxadiazole. In fact, the observed reactivities of the 3-*p*-nitrophenyl (**3d**), 3-*p*-methoxyphenyl (**3e**), and 3-phenyl (**3a**) derivatives follow the order **3d** > **3a** > **3e**. Consequently, the low reactivity observed in the case of **3f** can be explained on the basis of the combination of two negative effects: the steric hindrance of the perfluoroheptyl group and the electronic effect of the *p*-methoxyphenyl substituent. Interestingly, the order of the overall reaction rate (p-$O_2NC_6H_4 > C_6H_5 > p$-$MeOC_6H_4$) is exactly the opposite of the order of the relative stabilities of **4a**,**d**,**e** with respect to **3a**,**d**,**e**.

To confirm the proposed mechanism (Scheme 2) and to rationalize the observed order of reactivities, we also performed some calculations on the geometry of the supposed intermediates **7a**,**d**,**e** by assuming an actual (*Z*)/(*E*) arrangement for the bis(amide oxime) group. Interestingly, we found that the distance between the oxygen atom of the newly formed oxime group [C(5)=N−OH] and the electrophilic carbon atom of the second oxime group [C(3)=N−OH] is ca. 2.95 Å, a distance that allows intramolecular attack to occur. Moreover the total charge of the C(3)=NOH system (the electrophilic center) shifts from +0.013 for **7d** (R = p-$O_2NC_6H_4$) to 0.000 for **7a** (R = C_6H_5) and to −0.016 for **7e** (R = p-$MeOC_6H_4$), which is evidence that the highest electrophilic character is expected for the case of the p-O_2N derivative.

Conclusion

The reaction of various 5-perfluoroalkyl-1,2,4-oxadiazoles (**3a**−**g**) with hydroxylamine has been investigated in depth. The experimental results and the proposed mechanism are in very good agreement with ab initio computational data. This reaction represents the first example of an irreversible ring-degenerate rearrangement occurring on five-membered heterocycles by attack of an external bidentate nucleophile; more-

over, it allows the synthesis of compounds that are otherwise quite difficult to obtain. The usefulness, previously suggested in our articles,[4−6] of 5-perfluoroalkyl-1,2,4-oxadiazoles as ideal substrates for this kind of reactions has now been fully supported by theoretical considerations. Moreover, the reported computational data represent the first complete set of relative energies for substituted 1,2,4-oxadiazole regioisomers and turn out to be very useful for understanding the reaction's features as well as the behavior of 1,2,4-oxadiazoles.

Because of the large interest in 1,2,4-oxadiazoles as pharmaceuticals,[1,30] some further comments on the synthetic utility of this reaction are necessary. It is well known that the two most widely used methods of synthesizing 1,2,4-oxadiazoles are the amide oxime route (using different acylating reagents and subsequent cyclodehydration reactions)[16,31,32] and the nitrile oxide cycloaddition route.[16,31] Using these routes, the synthesis of 3-perfluoroalkyl-1,2,4-oxadiazoles **4** should involve the acylation/dehydration of fluorinated amide oximes or require the availability of a fluorinated nitrile oxide (or a chloro oxime as its precursor) to be used in a cycloaddition pattern.[33] These compounds, however, are not always easy to generate and, in some cases, the literature suggests that very harsh conditions are required for heterocyclization reactions of *O*-acyl derivatives of fluorinated amide oximes.[33] In contrast, the 5-perfluoroalkyl-substituted oxadiazoles are now readily accessible in a general way; in fact, their synthesis previously would imply an acylation/dehydration reaction of an amide oxime with a fluorinated acylating reagent.[33] Thereby, readily accessible 5-perfluoroalkyl-1,2,4-oxadiazoles can be considered very efficient synthons for the synthesis of the corresponding 3-perfluoroalkyl-substituted 1,2,4-oxadiazoles through the reaction with hydroxylamine that, inter alia, occurs under very mild conditions to afford excellent yields of the desired product.

Experimental Section

Materials and Methods: Melting points were determined with a Reichart-Thermovar hot-stage apparatus and are uncorrected. ^{1}H NMR spectra, recorded with a Bruker AC 250 E spectrometer, were taken using TMS as the internal standard. GC/MS and HRMS analyses were carried out using a VARIAN STAR 3400 CX/SATURN 2000 system and a VG70 70E apparatus, respectively. Flash chromatography was performed by eluting with mixtures of light petroleum (fraction boiling in the 40−60 °C range) and ethyl acetate of varying composition. Dry toluene (from Romil Pure Chemicals) and DMF (from Aldrich) were used as received. Compounds **3a**,[34] **3b**,[33b] **3c**,[33b] and **3g**[5] were prepared as reported. Compounds **3d**,[33h] **3e**,[33h] and **3f** were prepared by a similar procedure. Thus, a mixture of the appropriate amide oxime (10 mmol) and trifluoroacetic anhydride (in the case of compounds **3d** and **3e**: 1.5 mL, 11 mmol) or pentadecafluorooctanoyl chloride (2.7 mL, 11 mmol) in anhydrous toluene (100 mL) was heated under reflux for 3 h. After evaporation of the solvent, the residue was treated with water and then extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was evaporated under reduced pressure. Chromatography of the residue gave 3-(*p*-nitrophenyl)-5-trifluoromethyl-1,2,4-oxadiazole (**3d**; 70%), 3-(*p*-methoxyphenyl)-5-trifluoromethyl-1,2,4-oxadiazole (**3e**; 41%), and 3-(*p*-methoxyphenyl)-5-perfluoroheptyl-1,2,4-oxadiazole (**3f**; 55%).

Compound 3d: M.p. 63 °C (colorless crystals from light petroleum). ^{1}H NMR ($CDCl_3$): δ = 8.32−8.44 (m) ppm. MS: *m*/*z* = 259 (93) [M^+], 229 (100), 201 (67), 144 (19), 116 (23), 106 (28), 69 (59). $C_9H_4F_3N_3O_3$: calcd. C 41.71, H 1.56, N 16.22; found C 41.58, H 1.52, N 16.09.

Compound 3e: M.p. 42 °C (colorless crystals from light petroleum). ^{1}H NMR ($CDCl_3$): δ = 3.91 (s, 3 H), 7.17−7.22 (m, 2 H), 8.03−8.07 (m, 2 H) ppm. MS: *m*/*z* = 244 (100) [M^+], 175 (22), 147 (29), 106 (14). $C_{10}H_7F_3N_2O_2$: calcd. C 49.19, H 2.89, N 11.47; found C 49.06, H 2.85, N 11.36.

Compound 3f: M.p. 75−76 °C (colorless crystals from light petroleum). ^{1}H NMR ($CDCl_3$): δ = 3.89 (s, 3 H), 7.01−7.05 (m, 2 H), 8.05−8.09 (m, 2 H) ppm. MS: *m*/*z* = 544 (100) [M^+], 174 (18), 146 (28). $C_{16}H_7F_{15}N_2O_2$: calcd. C 35.31, H 1.30, N, 5.15; found C 35.17, H 1.28, N 5.13.

General Procedure for the Reaction of 5-Perfluoroalkyl-1,2,4-oxadiazoles (3a−g) with Hydroxylamine in DMF: A sample of **3a−g** (1.5 mmol) was added to a solution of hydroxylamine hydrochloride (0.31 g, 4.5 mmol) and potassium *tert*-butoxide (0.5 g, 4.5 mmol) and then the mixture was left at room temperature until the starting material was consumed (TLC). After dilution with water, the mixture was extracted with EtOAc. The combined extracts were dried and concentrated. Chromatography of the residue gave **4a−c** and **4e−g**. In the case of **3d**, filtration of insoluble material gave **4d** directly (Table 2). All new compounds gave correct elemental analyses (C, H, N).

Acknowledgments

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Table 2. Perfluoroalkyl-1,2,4-oxadiazoles **4a−g**

Products	M.p. [°C]	^{1}H NMR ($CDCl_3$/TMS) δ [ppm] (*J* [Hz])	HRMS or MS *m*/*z* (%)
4a[a]	15−16		
4b	oil	7.55−7.72 (m, 3 H), 8.19−8.22 (m, 2 H)	314 (100) [M^+], 195 (3), 103 (10)
4c	28−32[b]	7.55−7.71 (m, 3 H), 8.19−8.23 (m, 2 H)	calcd. 514.01623; found 514.01583
4d	104	8.39−8.48 (m)	calcd. 259.02048; found 259.02026
4e	49−50[b]	3.92 (s, 3 H), 7.04−7.08 (m, 2 H), 8.12−8.16 (m, 2 H)	calcd. 244.04596; found 244.04573
4f	90−91[b]	3.92 (s, 3 H), 7.03−7.08 (m, 2 H), 8.13−8.17 (m, 2 H)	calcd. 544.02680; found 544.02658
4g	oil	0.89 (t, *J* = 7, 3 H), 1.20−1.40 (m, 16 H), 1.80−1.92 (m, 2 H), 2.98 (t, *J* = 7, 2 H)	292 (16) [M^+], 262 (30), 220 (44), 164 (52), 152 (52), 54 (72), 40 (100)

[a] Ref.[33d] [b] Crystallization solvent: light petroleum (fraction boiling between 40 and 60 °C).

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