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Five-to-Six Membered Ring-Rearrangements in the Reaction of 5-Perfluoroalkyl-1,2,4-oxadiazoles with Hydrazine and Methylhydrazine

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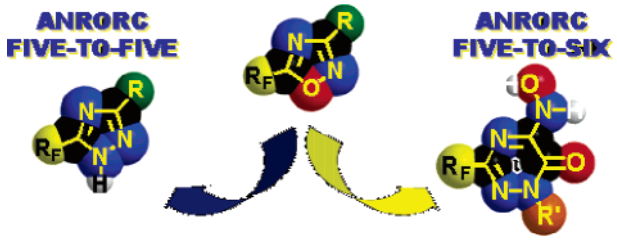

The hydrazinolysis reaction of 5-perfluoroalkyl-1,2,4-oxadiazoles with hydrazine or methylhydrazine as bidentate nucleophiles has been investigated. The reaction occurred through the addition of the bidentate nucleophile to the C(5)−N(4) double bond of the 1,2,4-oxadiazole followed by ring-opening and ring-closure (ANRORC) involving the second nucleophilic site of the reagent. This ring-closure step could involve either the original C(3) of the 1,2,4-oxadiazole (giving a five-to-five membered ring rearrangement) or an additional electrophilic center linked to it (exploiting a five-to-six membered ring rearrangement). An alternative initial nucleophilic attack may involve the additional electrophilic center linked at C(3), that is the carbonyl group, leading to the formation of the hydrazones which undergo the Boulton−Katritzky rearrangement (BKR). The chosen reaction path is a function of the used nucleophile and of the nature of the substituent at C(3). At variance with previous hypotheses, when methylhydrazine was used, the observed regiochemistry always showed the preferred initial attack by the less hindered NH_2 end of the nucleophile on C(5). Moreover, new spectroscopic evidence allowed the assignment of correct structures to the products formed by reaction of 5-perfluoroalkyl-3-phenyl-1,2,4-oxadiazoles with methylhydrazine.

Introduction

Heterocyclic rearrangements represent an interesting research field since in several cases they allow us to obtain other heterocyclic structures which are difficult to synthesize through the classical methodologies.[1,2] In this context, ANRORC processes (consisting of an initial nucleophilic attack followed by ring-opening and ring-closure) represent an useful tool, in the hand of the synthetic heterocyclic chemist, to achieve the ring transformation of heterocyclic systems.[2]

ANRORC reactions of π-deficient six-membered heterocycles, such as di- and triazines, have been extensively studied by Van der Plas and co-workers.[2] On the other hand, few

(1) See for example: (a) Boulton, A. J.; Katritzky, A. R.; Hamid, A. M. *J. Chem. Soc. C* **1967**, 2005−2007. (b) Afridi, A. S.; Katritzky, A. R.; Ramsden, C. A. *J. Chem. Soc., Perkin Trans. 1* **1976**, 315−320. (c) Ruccia, M.; Vivona, N.; Spinelli, D. *Adv. Heterocycl. Chem.* **1981**, *29*, 141−169. (d) L'abbé, G. *J. Heterocycl. Chem.* **1984**, *21*, 627−638. (e) Vivona, N.; Buscemi, S.; Frenna, V.; Cusmano, G. *Adv. Heterocycl. Chem.* **1993**, *56*, 49−154. (f) Pace, A.; Pibiri, I.; Buscemi, S.; Vivona, N. *Heterocycles* **2004**, *63*, 2627−2648.

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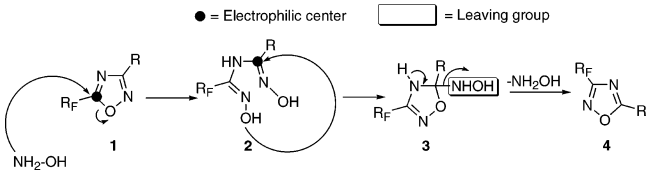
SCHEME 1. Ring-Degenerate ANRORC Rearrangement of 5-Perfluoroalkyl-1,2,4-oxadiazoles



examples of ANRORC rearrangements are reported for five-membered heterocycles. These include electron poor five-membered systems such as 1,3,4-oxadiazoles,[3] 1,3,4-thiadiazoles,[4] nitroimidazoles,[3,5] and the recently reported bis(1,3,4-thiadiazol-2-yl)-1,3,5-triazinium halides.[6]

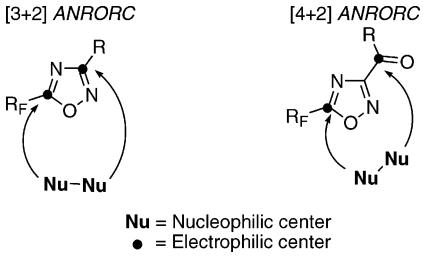
In general, one may assume that the ANRORC reactivity depends on three main factors: (i) the electrophilic character of the heterocyclic ring which can make possible or prevent the initial nucleophilic attack; (ii) the presence of a further electrophilic center in the *open-chain* intermediate (formed during the ring-opening stage) which allows the cyclization step; (iii) the presence of good leaving groups which allows the final elimination processes to occur, furnishing compounds thermodynamically favored with respect to the starting materials.

For five-membered heterocycles, the first factor is a function of the number of pyridine-like nitrogens in the ring and of the electron withdrawing ability (and location) of the substituents. As for the electrophilic center and the leaving group, they can either be generated during the ring-opening process or be already part of some substituent on the starting ring.

On the basis of the above considerations, we recently studied the ring-degenerate rearrangements of 5-perfluoroalkyl-1,2,4-oxadiazoles **1** into their corresponding 3-perfluoroalkyl-regioisomers **4** by performing an ANRORC reaction with hydroxylamine as a bidentate nucleophile.[7] In this reaction, the electron-poor and weakly aromatic 1,2,4-oxadiazole[8,9] is even more activated, toward a nucleophilic attack, by the presence of the strongly electron-withdrawing perfluoroalkyl group at C(5).

In this reaction a second electrophilic center is created, after the ring-opening step, on the original C(3) of the starting ring. This center is attacked, in the ring closure step, by the oxygen end of the bidentate nucleophile. Finally, in the rearomatization step the hydroxylamino moiety (originally part of the oxadiazole ring) acts as the leaving group (Scheme 1). This reaction, which can be classified as a [3 + 2] ANRORC heterocyclization (Chart 1), is irreversible since the obtained 3-perfluoroalkyl-1,2,4-oxadiazoles, which are more stable than the starting 5-perfluoroalkyl-regioisomers[7] (at room temperature the eventual equilibrium constant is larger than 10^3), are not activated toward ANRORC.

CHART 1. ANRORC Rearrangements of 5-Perfluoroalkyl Oxadiazoles with Bidentate Nucleophiles.



To enlarge the synthetic applications of this ANRORC approach, hydrazine and methylhydrazine could also be used as bidentate nucleophiles. It is noteworthy that, besides the regiochemistry issues due to the use of an unsymmetrical bidentate nucleophile such as methylhydrazine, the presence of another electrophilic center within the C(3) substituent introduces other potential competitive paths such as [4 + 2] ANRORC cyclizations (Chart 1).

Preliminary results on the reaction of 5-perfluoroalkyl-1,2,4-oxadiazoles with hydrazine showed the formation of 1,2,4-triazoles from a [3 + 2] ANRORC rearrangement.[10] In the case of 3-benzoyl-5-perfluoroalkyl-1,2,4-oxadiazoles the presence of a side-chain electrophilic center shifted the reaction toward a [4 + 2] ANRORC rearrangement into triazinone oximes (Chart 1).[11] In this work we report a complete set of reactions with hydrazines, which includes the new interesting reactivity observed for 3-ethoxycarbonyl-5-perfluoroalkyl-1,2,4-oxadiazoles. As for the reaction with methylhydrazine, we will discuss the observed reactivity as a function of the substituent at C(3) and point out the differences with respect to the reaction with hydrazine. Moreover, a reinvestigation, based on new spectroscopic evidence, of the reaction of 3-phenyl-5-perfluoroalkyl-1,2,4-oxadiazoles with methylhydrazine allowed an assignment of the correct structure to the formed products.

Results and Discussion

The ANRORC behavior has been studied considering 3-substituted-5-perfluoroalkyl-oxadiazoles where the C(3) substituent was (i) nonelectrophilic, (ii) containing an electrophilic center, or (iii) containing a leaving group linked to an electrophilic center. In the following paragraphs, all the possible reaction pathways are illustrated as a function of the substituent at C(3) or of the used nucleophile. Considering the number of possible products that could be formed during the studied reactions, the observed selectivity is, in some cases, extremely significant and is discussed below.

Reactions of 3-Aryl-5-perfluoroalkyl-1,2,4-oxadiazoles with Hydrazine and Methylhydrazine. For 1,2,4-oxadiazoles **5** (Scheme 2), where the C(3) substituent does not contain an electrophilic center, the initial attack of the nucleophile can occur only at C(5) of the oxadiazole ring. In the reaction with hydrazine[10,12] we have reported the formation of triazoles **8** (tautomers of **13**) together with some amounts of 3-perfluoro-

(2) Van der Plas, H. C. *Adv. Heterocycl. Chem.* **1999**, *74*, 1−253.
(3) (a) Hetzheim, A.; Möckel, K. *Adv. Heterocycl. Chem.* **1966**, *7*, 183−224. (b) Reid, J. R.; Heindel, N. D. *J. Heterocycl. Chem.* **1976**, *13*, 925−926.
(4) Sandström, J. *Adv. Heterocycl. Chem.* **1968**, *9*, 165−209.
(5) Suwinski, J.; Pawlus, W.; Salwinska, E.; Swierczek, K. *Heterocycles* **1994**, *37*, 1511−1520.
(6) Wermann, K.; Walther, M.; Günther, W.; Görls, H.; Anders, E. *Tetrahedron* **2005**, *61*, 673−685.
(7) Buscemi, S.; Pace, A.; Pibiri, I.; Vivona, N.; Lanza, C. Z.; Spinelli, D. *Eur. J. Org. Chem.* **2004**, 974−980.
(8) (a) Bird, C. W. *Tetrahedron* **1985**, *41*, 1409−1414. (b) Bird, C. W. *Tetrahedron* **1992**, *48*, 335−340.
(9) For aromaticity criteria of five-membered heterocycles, see also: (a) Bean, G. P. *J. Org. Chem.* **1998**, *63*, 2497−2506. (b) Katritzky, A. R.; Barczynski, P.; Musumarra, G.; Pisano, D.; Szafran, M. *J. Am. Chem. Soc.* **1989**, *111*, 7−15. (c) Katritzky, A. R.; Jug, K.; Oniciu, D. C. *Chem. Rev.* **2001**, *101*, 1421−1449. (d) Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. *Chem. Rev.* **2004**, *104*, 2777−2812.
(10) Buscemi, S.; Pace, A.; Pibiri, I.; Vivona, N.; Spinelli, D. *J. Org. Chem.* **2003**, *68*, 605−608.
(11) Buscemi, S.; Pace, A.; Palumbo Piccionello, A.; Macaluso, G.; Vivona, N.; Spinelli, D.; Giorgi, G. *J. Org. Chem.* **2005**, *70*, 3288−3291.

SCHEME 2. Hydrazinolysis of 5-Perfluoroalkyl-1,2,4-oxadiazoles 5

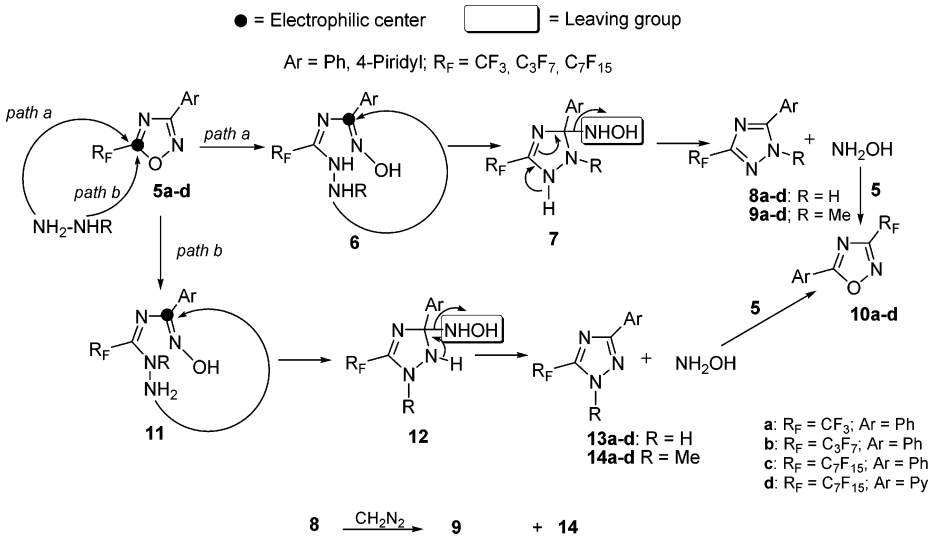


TABLE 1. Product Distribution (%) from the Reaction of 5 with Hydrazine (R = H) and Methylhydrazine (R = Me)

substrate	R_F	Ar	R	8	9	10
5a	CF_3	Ph	H	70[a]		10[b]
5b	C_3F_7	Ph	H	72[a]		11[b]
5c	C_7F_{15}	Ph	H	82[a]		15[b]
5d	C_7F_{15}	4-Py	H	65[c]		23[c]
5a	CF_3	Ph	Me		80[d]	19[b]
5b	C_3F_7	Ph	Me		75	24[b]
5c	C_7F_{15}	Ph	Me		71[d]	26[b]
5d	C_7F_{15}	4-Py	Me		85[c,e]	10[c]

[a] These results are in agreement with what previously reported within experimental errors.[10] [b] See ref 7. [c] See ref 12. [d] See ref 10. [e] In this reaction, the triazole regioisomer **14d**, originating from the initial attack of the *N*-methylated end of the nucleophile on the C(5) of the oxadiazole, has been isolated in 4% yield.[12]

alkyl-1,2,4-oxadiazoles **10** (see Table 1) formed by the reaction between the starting oxadiazoles **5** and the hydroxylamine eliminated during the main process.[7,13]

In the case of the reaction with methylhydrazine, the regioselectivity of the process (paths a or b in Scheme 2) is determined by which end of the nucleophile attacks the oxadiazole. In a previous communication we proposed the formation of triazoles **14a**−**c** and explained their formation through the initial attack of the more nucleophilic end of the nucleophile (path b in Scheme 2). However, a deeper spectroscopic investigation revealed that the structure of the formed triazoles was misassigned and that the correct structure was that of triazoles **9a**−**c**.[14] The regioselective formation of triazoles **9d** was also observed in the case of 3-(4′-pyridyl)-1,2,4-oxadiazoles **5d**, confirming that the initial attack at the C(5) preferentially involves the less hindered NH_2 end of the nucleophile (path a in Scheme 2).[12]

All three pairs of regioisomers (**9a**−**c** and **14a**−**c**) were then synthesized, through diazomethane methylation of the corresponding triazoles **8a**−**c**, for a structure correlation study. The ^{1}H ^{13}Cg-HMBC spectrum of **9a** revealed the presence of a long-range coupling between the methyl signal at 4.06 ppm and the quaternary carbon at 155.9 ppm. The same carbon has a similar coupling with the ortho hydrogens of the phenyl group at 7.83 ppm, so it can be assigned to the phenyl-substituted C(5) of the 1,2,4-triazole ring. On the other hand, the long range coupling has not been observed between the methyl hydrogens and the quaternary C(3) carbon at 150.9 ppm, easily recognizable as a quartet because of geminal C−F coupling ($^2J_{C-F}$ = 38.8 Hz) with the CF_3. These data allow the assignment of the 1-methyl-5-phenyl-3-trifluoromethyl-1,2,4-triazole structure to compound **9a**. The assignment of the ^{15}N chemical shifts of the methyl-substituted N(1) (206.9 ppm) and pyridine-like N(2) (302.2 ppm) were determined by observing the long-range coupling with the methyl hydrogens by means of ^{1}H ^{15}N g-HMBC spectra.[15] The remaining chemical shift of N(4) (248.9 ppm), lacking of any coupling with the protons, was determined from the ^{15}N spectrum.

In the case of **14a**, the ^{1}H ^{13}C g-HMBC spectrum showed a long range coupling between the methyl hydrogens signal at 4.10 ppm and the trifluoromethylated quaternary carbon at 143.8 ppm, easily recognizable as a quartet because of the geminal C−F coupling ($^2J_{C-F}$ = 40.6 Hz).

On the other hand, the ortho hydrogens of the phenyl group show long-range correlation with the other quaternary carbon [i.e., the C(3) at 160.1 ppm] of the 1,2,4-triazole ring. These data allow a satisfactory assignment of the 1-methyl-3-phenyl-5-trifluoromethyl-1,2,4-triazole structure to compound **14a** (see Supporting Information for the two ^{1}H ^{13}C g-HMBC spectra of compounds **9a** and **14a**). Also in this case the assignment of the ^{15}N chemical shifts of methyl-substituted N(1) (207.9 ppm) and pyridine-like N(2) (300.4 ppm) were obtained from ^{1}H ^{15}N g-HMBC, while the remaining N(4) shift (250.6 ppm) was determined from the ^{15}N NMR spectrum. The same approach was used to determine the structures of the other pairs of products **9b**,**c** and **14b**,**c**. The correct assignment has been also definitely confirmed by X-ray diffraction in the case of **9c** (see Supporting Information), showing that the methyl group is bonded to the nitrogen near the phenyl group, in agreement with the 1-methyl-3-perfluoroepthyl-5-phenyl-1,2,4-triazole structure.

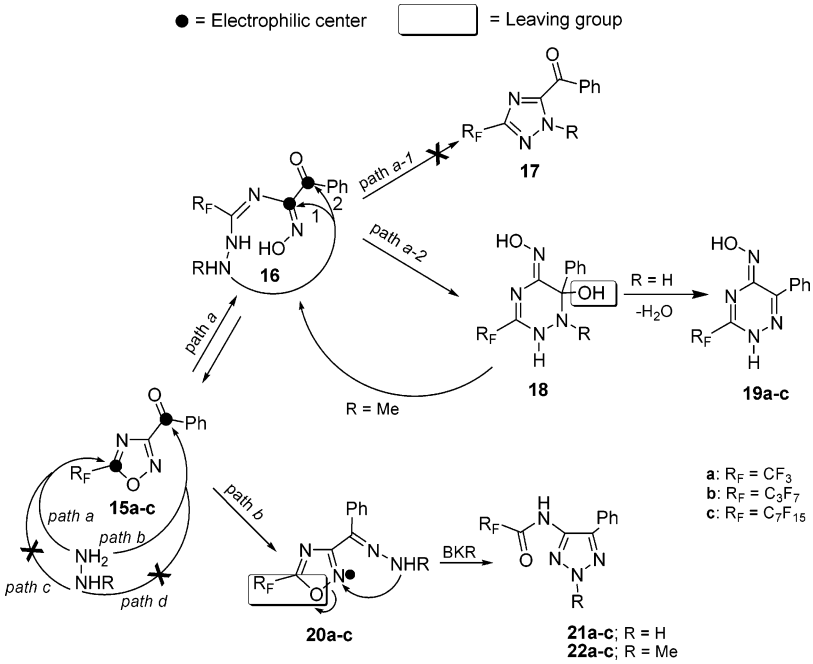
(12) Pibiri, I.; Pace, A.; Buscemi, S.; Vivona, N.; Malpezzi, L. *Heterocycles* **2006**, *68*, 307−321.

(13) In our preliminary communication[10] this product was reported as unidentified.

(14) Moreover, the previously reported formation of demethylated product **8a**,**c** depends on the purity degree of the used methylhydrazine reagent.[10]

(15) For a comprehensive review on long-range ^{1}H ^{15}N heteronuclear correlations and ^{15}N chemical shifts see: Martin, G. E.; Hadden, C. E. *J. Nat. Prod.* **2000**, *63*, 543−585

SCHEME 3. Hydrazinolysis of 5-Perfluoroalkyl-1,2,4-oxadiazoles Bearing an Electrophilic Substituent at C(3)



Reactions of 3-Benzoyl-5-perfluoroalkyl-1,2,4-oxadiazoles with Hydrazine and Methylhydrazine. As illustrated in the case of compounds **15**, when the 5-perfluoroalkyl-1,2,4-oxadiazole contained another electrophilic center on the substituent at C(3), several reaction pathways became available (Scheme 3). For a symmetric nucleophile such as hydrazine, paths a and b in Scheme 3 indicate the attack at the C(5) or at the carbonyl moiety, respectively. As previously reported, the reaction of oxadiazoles **15** with hydrazine[11] leads mainly to the triazinone oxime **19** (from path a-2) and to the Boulton−Katritzky rearrangement (BKR)[1a−c,e] product **21** (from path b). It is noteworthy that the yield of compound **21** significantly increased along with the steric bulkiness of the perfluoroalkyl group otherwise confirming, in the absence of steric hindrance, that the C(5) was the preferred site of the initial attack.[11]

The use of an asymmetric nucleophile introduces two additional possible paths (paths c and d in Scheme 3). Interestingly, in the reaction with methylhydrazine, no product was isolated from paths c or d, thus confirming that only the NH_2 end of the nucleophile is involved in the first attack. However in this case, differently from the reaction with hydrazine, the BKR product **22** (64−97%) was the only one obtained. A mechanistic explanation considers that in path a-2, the C(5) is still the preferred electrophilic site during the initial nucleophilic attack,[11] while the carbonyl is the preferred cyclization site. Probably the formation of **18** is a reversible process, that can be driven by the formation of the stable triazinone oxime **19** from tetrahydro triazine **18** through an elimination process which is only possible for R = H (i.e., in the reaction with hydrazine). Lacking this driving force, the reaction with methylhydrazine develops through path b leading exclusively to highly stable triazoles **22**[8,9] (see Table 2). This observation supports the hypothesis that the **15** → **16** → **18** transformation could be, at least in the first stage, reversible.

Reactions of 3-Carboxyethyl-5-perfluoroalkyl-1,2,4-oxadiazoles with Hydrazine and Methylhydrazine. The cyclization and the subsequent elimination are key reaction steps involving the side-chain carbonyl substituent. We therefore decided to investigate the effects of the presence of a leaving group at the carbonyl moiety and studied the reactivity of 3-carboxyethyl-5-perfluoroalkyl-1,2,4-oxadiazoles **23** with hydrazine and methylhydrazine (Scheme 4).

TABLE 2. Product Distribution (%) from the Reaction of 15 with Hydrazine (R = H) and Methylhydrazine (R = Me)

substrate	R_F	Ar	R	**19**	**21**	**22**
15a	CF_3	Ph	H	92[a]	5[a]	
15b	C_3F_7	Ph	H	70[a]	24[a]	
15c	C_7F_{15}	Ph	H	65[a]	29[a]	
15a	CF_3	Ph	Me			64
15b	C_3F_7	Ph	Me			75
15c	C_7F_{15}	Ph	Me			97

[a] See ref 11.

Despite the fact that the presence of the leaving group may introduce additional paths, we observed in both reactions with hydrazine and methylhydrazine, and for all oxadiazoles **23**, a surprising selectivity for the formation of triazinones **27** and **28** (from path a-2) which are isolated as the only products in 81−97% yield. Once again, the observed regioselectivity confirms the preferential attack of the NH_2 end of the methylhydrazine on the C(5). Moreover, path c (and the subsequent BKR) is shut down by the lower reactivity of the carboxyethyl group toward hydrazines in comparison with the benzoyl group in compound **15**. The cyclization step involves the carbonyl moiety of the open-chain intermediate **25**. However, unlike compound **18**, the presence of the ethoxy leaving group allows the final elimination process to occur independently from the nature of the R substituent (R = H, Me) present in the hydrazines.

Both NMR spectra and X-ray analysis were employed to unambiguously assign the structures of compounds **27a−c** and **28a−c**.

In the case of compounds **28a−c**, crystals suitable for X-ray diffraction were obtained for **28c** (see Supporting Information). From the X-ray data, however, the position of the NH group was not completely clear, owing to the very weak absorption

SCHEME 4. Hydrazinolysis of 5-Perfluoroalkyl-1,2,4-oxadiazoles Bearing an Electrophilic Substituent at C(3) Containing a Leaving Group

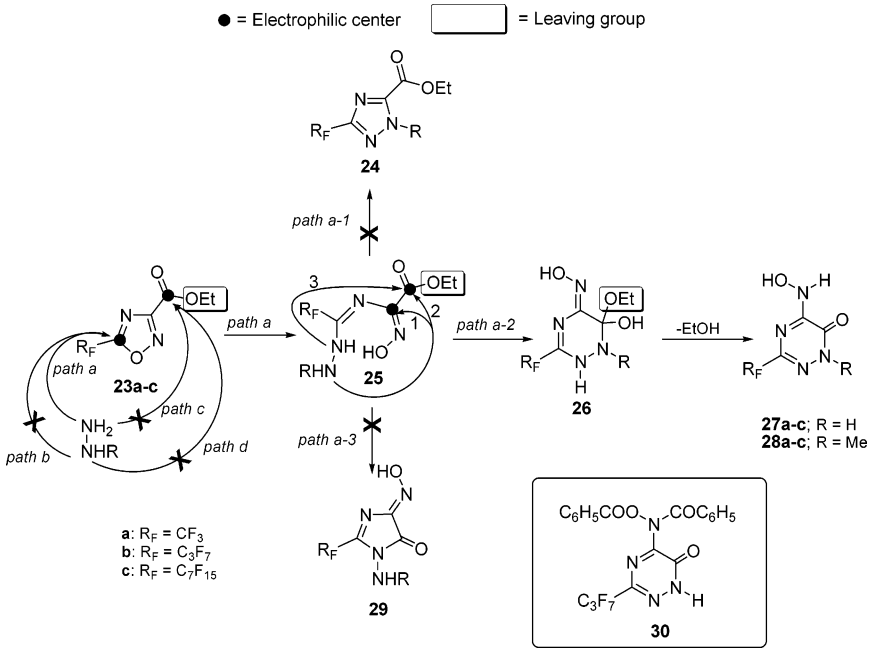
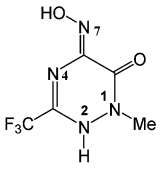
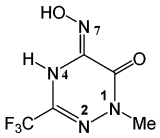
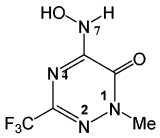


TABLE 3. Ab initio Calculated Chemical Shift (GIAO Method at the B3LYP/6-311++G(2d,p)//B3LYP/6-311G(d) Level)[a] and Relative Energies Calculated for 28a

tautomer	N_1	N_2	N_4	N_7	Mean Abs. Dev. (ppm)[b]	Rel. Energy (kcal mol^{-1})
 **28-2NH**	167	157	239	425	109	19.2
 **28-4NH**	204	294	132	355	77	3.4
 **28-5CNHOH**	221	311	225	185	29	0
Exp **28c**	185.4	275.2	205.1	159.6	-	-

[a] Reference was NH_3, calculated at the same level of theory. [b] The reported values were obtained by the sum of the absolute value of the difference between the calculated shift and the experimental one.

of the crystals. Since there are, in theory, three possible tautomeric forms available to **28** (indicated as **28−2NH**, **28−4NH**, and **28−5CNHOH**; see Table 3) in order to resolve this ambiguity, both direct detected ^{15}N spectra and ^{1}H ^{15}N g-HMBC spectra were acquired for **28c**, and ab initio chemical shift calculation (GIAO method at the B3LYP/6-311G++(2d,p)// B3LYP/6-311G(d) level)[16] were obtained for all the three tautomeric forms of **28a** (see Table 3).[17] In the ^{15}N spectrum, the four signals of **28c** were observed at 159.6, 185.4, 205.1, and 275.2 ppm; from the ^{1}H-^{15}N long-range correlation spectrum, the two nitrogen atoms in positions 1 and 2, because of their long-range coupling with the methyl hydrogens, were assigned to the signals at 185.4 and 275.2 ppm, respectively. The latter chemical shift is typical of a pyridine-like nitrogen, while the signal at 185.4 ppm corresponds to the methylated pyrrole-like nitrogen in position 1.[15] The presence of the methyl

in position 1 is evident from X-ray data, and also from ^{1}H ^{13}C HMBC spectrum, where it is evident in the long range coupling of the methyl hydrogens with the carbonyl carbon. These data imply that the NH group cannot be located in position 2 of the triazinone ring, thus the **28**−**2NH** form can be excluded.

In the case of the two remaining structures (i.e., **28**−**4NH** and **28**−**5CNHOH** in Table 3), the main difference lies in the electronic distribution around the oximic nitrogen. Because of the simultaneous presence of the double bond and of the oxygen, the oximic nitrogen is usually found at very low field[18] (from 345 to 365 ppm), while in the present case its chemical shift should be assigned to one of the signals at 205.1 or 159.6 ppm. In the case of the hydroxilaminic form **28**−**5CNHOH**, the expected chemical shift[19] is much more compatible with the observed spectra. Indeed, also the chemical shift obtained from ab initio calculations for the three tautomers of **28a** show the best agreement in the case of the **28**−**5CNHOH** structure; incidentally this tautomer is also calculated to be the most stable. Further support to this hypothesis comes from the comparison between the experimentally, X-ray derived, bond distances for **28c** and the calculated ones for **28a**, from which it is evident the single-bond nature of the C(5)−NHOH bond (see Supporting Information for a comparison between the two structures).

In the case of compound **27c**, the ^{1}H NMR and ^{13}C NMR spectra show three very broad signals for the three protons and for the three quaternary carbons, and no heteronuclear correlations were observed in both ^{1}H ^{15}N HMBC and ^{1}H ^{13}C HMBC spectra. These data indicate that a chemical exchange between different species is fast in the NMR time scale. In the case of **27c**, in addition to the three tautomeric forms already shown for **28a**−**c**, each of them could be present in the C(6)−OH form. Lacking any indication from NMR data, and being impossible for us to produce good crystals for these compounds, compound **27b** was subjected to aroylation with benzoyl chloride. The resulting compound **30** yielded good crystals, suitable for the X-ray diffraction analysis. X-ray data (see Supporting Information) show that compound **30** derives from the hydroxylamino form. The X-ray data further confirms the presence of the hydroxylamino form in the case of **28a**−**c**, indeed the bond distance C−N(7) is 1.39 Å, to be compared with the experimentally observed distance of 1.38 Å in the case of **28c**.

(16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

(17) To reduce the computational time, the ab initio chemical shift calculations were obtained for compound **28a**, in which the only difference with **28c** is the presence of a CF_3 group instead of the C_7F_{15} chain.

(18) Kolehmainen, E.; Gawinecki, R.; Oœmialowski, B. Trezbiatowska, K. *Magn. Reson. Chem.* **1997**, *35*, 778−784.

(19) For example the ^{15}N chemical shift of *N*-benzyl-hydroxylamine and *N*,*N*-dimethyl-hydroxylamine were found to be 126.1 and 145.1 ppm, respectively (in DMSO-d_6, this work).

Conclusions

Among the plethora of nonphotochemical heterocyclic rearrangements, which are usually carried out by using harsh thermal conditions, ANRORC rearrangements on activated 5-perfluoroalkyl-1,2,4-oxadiazoles resulted in a very versatile and mild method to synthesize fluorinated 1,2,3- and 1,2,4-triazoles, *Z*-oximes of 1,2,4-triazin-5-ones and 5-hydroxylamino-1,2,4-triazin-6-ones.

The study, carried on different hydrazinolysis reactions with hydrazine and methylhydrazine on differently substituted substrates, allowed us to rationalize the results obtained considering the factors involved in all the steps of the ANRORC process in terms of (i) the initial attack by the less hindered side of the bidentate nucleophile; (ii) the steric influence of the perfluoroalkyl group and the extent of the electronic demand in the competition between the C(5) of the oxadiazole ring and the side-chain carbonyl group in undergoing the initial nucleophilic attack; (iii) the competition between the C(3) of the oxadiazole and the side-chain carbonyl group in undergoing the second nucleophilic attack (i.e., in the cyclization step); and (iv) the evolution of reaction intermediates as a function of the leaving group ability of the substituent on the side-chain electrophilic site. Despite the fact that several paths were available, the observed regioselectivity was fairly good and opens the way to future developments of this strategy for the obtainment of other fluorinated heterocycles.

Experimental Section

General Procedure for the Hydrazinolysis of 5-Perfluoroalkyl-3-phenyl-1,2,4-oxadiazoles 5a−c with Hydrazine or Methylhydrazine in DMF. To a sample of compunds **5a**−**c** (1.5 mmol) in dry DMF (2 mL) was added an excess of hydrazine or methylhydrazine (7.5 mmol), and the mixture was left at room temperature for 1 h (for **5a,b**) or 10 h (for **5c**). After dilution with water, the mixture was extracted with EtOAc, which was dried and evaporated, and the residue was chromatographed. Results are reported in Table 1.

Hydrazinolysis of the 5-Heptafluoropropyl-3-phenyl-1,2,4-oxadiazole 5b with Methylhydrazine. Compound **9b** is an oil. ^{1}H NMR (599.7 MHz, DMSO-d_6, 25 °C): δ 4.09 (s, 3H), 7.59−7.64 (m, 3H), 7.83 (m, 2H). ^{13}C NMR (150.8 MHz, DMSO-d_6, 25 °C ^{1}H decoupled): δ 37.9 (Me), 108.8 (tq, $^1J_{C-F}$ = 266.4, $^2J_{C-F}$ = 37.4 Hz, CF_2), 110.5 (tt, $^1J_{C-F}$ = 254.3, $^2J_{C-F}$ = 31.5 Hz, CF_2), 117.1 (qt, $^1J_{C-F}$ = 289.3, $^2J_{C-F}$ = 35.5 Hz, CF_3), 126.2 (Cq), 128.8 (2 CH), 128.9 (2 CH), 130.8 (CH), 150.0 (t, J_{C-F} = 28.2 Hz, Cq), 156.2 (Cq). ^{19}F NMR (564.2 MHz, DMSO-d_6, 25 °C): δ −126.5 (bs, 2F), −112.1 (q, 2F, J = 8.1 Hz), −79.8 (t, 3F, J = 8.2 Hz). ^{15}N NMR (60.8 MHz, DMSO-d_6, 25 °C): δ 209.0, 251.6, 305.4. HRMS: calcd for $C_{12}H_8F_7N_3$, 327.06066; found, 327.05999.

General Procedure for the Methylation of 5-Perfluoroalkyl-3-phenyl-1,2,4-triazoles 8a−c with Diazomethane. To a sample of compounds **8a**−**c** (0.5 mmol) in diethyl ether (10 mL), an ethereal solution of CH_2N_2 was added, and the solution was allowed to stir at room temperature for 1 h. After removal of the solvent, the residue was chromatographed.

Methylation of 5-Trifluoromethyl-3-phenyl-1,2,4-triazole 8a. Chromatography of the residue gave 1-methyl-3-phenyl-5-trifluoromethyl-1,2,4-triazole **14a** (72%) and 1-methyl-3-trifluoromethyl-5-phenyl-1,2,4-triazole **9a** (25%).[10]

Compound 9a. ^{1}H NMR (599.7 MHz, DMSO-d_6, 25 °C): δ 4.06 (s, 3H), 7.57−7.64 (m, 3H), 7.83 (m, 2H). ^{13}C NMR (150.8 MHz, DMSO-d_6, 25 °C ^{1}H decoupled): δ 37.7 (Me), 119.4 (q, J_{C-F} = 269.2 Hz, CF_3), 126.3 (Cq), 128.7 (2 CH), 128.8 (2 CH), 130.7 (CH), 150.9 (q, J_{C-F} = 38.8 Hz, Cq), 155.9 (Cq). ^{19}F NMR (564.2 MHz, DMSO-d_6, 25 °C): δ −64.4. ^{15}N NMR (60.8 MHz,

DMSO-d_6, 25 °C): δ 206.9, 248.9, 302.2. HRMS: calcd for $C_{10}H_8F_3N_3$, 227.06704; found, 227.06644.

Compound 14a. mp 83−85 °C (from light petroleum). ^{1}H NMR (599.7 MHz, DMSO-d_6, 25 °C): δ 4.10 (s, 3H), 7.46−7.53 (m, 3H), 8.01 (m, 2H). ^{13}C NMR (150.8 MHz, DMSO-d_6, 25 °C ^{1}H decoupled): δ 37.3 (Me), 118.5 (q, J_{C-F} = 267.8 Hz, CF_3), 125.8 (2 CH), 128.9 (2 CH), 129.2 (Cq), 129.9 (CH), 143.8 (q, J_{C-F} = 40.6 Hz, Cq), 160.1 (Cq). ^{19}F NMR (564.2 MHz, DMSO-d_6, 25 °C): δ −62.0. ^{15}N NMR (60.8 MHz, DMSO-d_6, 25 °C): δ 207.9, 250.6, 300.4. HRMS: calcd for $C_{10}H_8F_3N_3$, 227.06704; found, 227.06654.

Methylation of 5-Heptafluoropropyl-3-phenyl-1,2,4-triazole 8b. Chromatography of the residue gave 5-heptafluoropropyl-1-methyl-3-phenyl-1,2,4-triazole **14b** (72%) and 3-heptafluoropropyl-1-methyl-5-phenyl-1,2,4-triazole **9b** (19%).

Compound 14b. mp 65−66 °C (from light petroleum). ^{1}H NMR (599.7 MHz, DMSO-d_6, 25 °C): δ 4.12 (s, 3H), 7.47−7.53 (m, 3H), 8.01 (m, 2H). ^{13}C NMR (150.8 MHz, DMSO-d_6, 25 °C ^{1}H decoupled): δ 37.9 (Me), 108.8 (tq, $^1J_{C-F}$ = 266.4, $^2J_{C-F}$ = 36.8 Hz, CF_2), 110.5 (tt, $^1J_{C-F}$ = 256.8, $^2J_{C-F}$ = 32.6 Hz, CF_2), 117.1 (qt, $^1J_{C-F}$ = 288.4, $^2J_{C-F}$ = 33.4 Hz, CF_3), 125.8 (2 CH), 128.9 (2 CH), 129.0 (Cq), 130.0 (CH), 142.4 (t, J_{C-F} = 29.7 Hz, Cq), 160.7 (Cq). ^{19}F NMR (564.2 MHz, DMSO-d_6, 25 °C): δ −126.0 (bs, 2F), −110.7 (q, 2F, J = 8.2 Hz), −79.6 (t, 3F, J = 8.2 Hz). ^{15}N NMR (60.8 MHz, DMSO-d_6, 25 °C): δ 210.6, 253.1, 302.0. HRMS: calcd for $C_{12}H_8F_7N_3$, 327.06066; found, 327.06014.

Methylation of 5-Pentadecafluoroheptyl-3-phenyl-1,2,4-triazole 8c. Chromatography of the residue gave 1-methyl-3-phenyl-5-pentadecafluoroheptyl-1,2,4-triazole **14c** (72%) and 1-methyl-3-pentadecafluoroheptyl-5-phenyl-1,2,4-triazole **9c** (25%).[10]

Compound 9c. ^{1}H NMR (599.7 MHz, DMSO-d_6, 25 °C): δ 4.03 (s, 3H), 7.51−7.58 (m, 3H), 7.78 (m, 2H). ^{13}C NMR (150.8 MHz, DMSO-d_6, 25 °C ^{1}H decoupled): δ 37.8 (Me), 126.2 (Cq), 128.6 (2 CH), 128.8 (2 CH), 130.7 (CH), 150.4 (t, J_{C-F} = 28.5 Hz, Cq), 156.0 (Cq). ^{13}C NMR (150.8 MHz, DMSO-d_6, 25 °C ^{19}F decoupled): δ 108.5, 110.4, 110.9 (2 signals), 111.3, 112.1, 117.2 (CF_3). ^{19}F NMR (564.2 MHz, DMSO-d_6, 25 °C): δ −126.9, −123.5, −122.8 (2 signals), −122.2, −112.1, −81.7 (CF_3). ^{15}N NMR (60.8 MHz, DMSO-d_6, 25 °C): δ 208.5, 251.7, 305.5. HRMS: calcd for $C_{16}H_8F_{15}N_3$, 527.04790; found, 527.04788.

Compound 14c. mp 65−67 °C (from light petroleum). ^{1}H NMR (599.7 MHz, DMSO-d_6, 50 °C): δ 4.11 (s, 3H), 7.47−7.52 (m, 3H), 8.00 (m, 2H).^{13}C NMR (150.8 MHz, DMSO-d_6, 50 °C ^{1}H decoupled): δ 37.8 (Me), 125.7 (2 CH), 128.7 (2 CH), 129.0 (Cq), 129.8 (CH), 142.4 (t, J_{C-F} = 29.9 Hz, Cq), 160.4 (Cq). ^{13}C NMR (150.8 MHz, DMSO-d_6, 50 °C ^{19}F decoupled): δ 107.7, 109.6, 110.1, 110.2, 110.5, 111.0, 116.4 (CF_3). ^{19}F NMR (564.2 MHz, DMSO-d_6, 50 °C): δ −126.0, −122.7, −122.0, −121.4, −121.3, −119.7, −80.7 (CF_3). ^{15}N NMR (60.8 MHz, DMSO-d_6, 50 °C): δ 207.9, 250.6, 300.4. HRMS calcd for $C_{16}H_8F_{15}N_3$, 527.04790; found, 527.04756.

General Procedure for the Synthesis of 3-Carboxyethyl-5-perfluoroalkyl-1,2,4-oxadiazoles 23a−c. A mixture of carboxyethyl amidoxime (1.32 g; 10 mmol) in pyridine (30 mL) and the appropriate polyfluoroalkyl chloride (22 mmol) was stirred for 8 h at room temperature. After removal of the solvent, the residue was treated with water and then extracted with Et_2O. The organic layer was dried over Na_2SO_4 and evaporated. Chromatography of the residue gave the oxadiazoles **23a−c**.

3-Carboxyethyl-5-trifluoromethyl-1,2,4-oxadiazole 23a. Yield 84%; colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.46 (t, 3H, J = 7.5 Hz), 4.54 (q, 2H, J = 7.5 Hz). GC-MS *m/z*: 211 (M^++ 1, 100), 183 (15), 100 (12), 70 (35). IR (Nujol): 1763 cm^{-1}. Anal. Calcd for $C_6H_5N_2O_3F_3$: C, 34.30; H, 2.40; N, 13.33. Found: C, 34.50; H, 2.30; N, 13.20.

3-Carboxyethyl-5-hepthafluoropropyl-1,2,4-oxadiazole 23b. Yield 65%; colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.48 (t, 3H, J = 7.0 Hz), 4.57 (q, 2H, J = 7.0 Hz). GC-MS *m/z:* 311 (M^+ + 1, 100), 283 (11), 265 (59), 100 (8), 70 (28). IR (Nujol): 1763 cm^{-1}. Anal. Calcd for $C_8H_5N_2O_3F_7$: C, 30.98; H, 1.63; N, 9.03. Found: C, 30.80; H, 1.80; N, 9.20.

3-Carboxyethyl-5-pentadecafluoroheptyl-1,2,4-oxadiazole 23c. Yield 64%; colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.47 (t, 3H, J = 7.5 Hz), 4.56 (q, 2H, J = 7.5 Hz). GC-MS *m/z* 511 (M^++1, 72), 510 (M^+, 11), 484 (41), 466 (88), 119 (28), 100 (36), 69 (100), 45 (19). IR (Nujol) 1763 cm^{-1}. Anal. Calcd for $C_{12}H_5N_2O_3F_{15}$: C, 28.25; H, 0.99; N, 5.49. Found: C, 28.30; H, 1.00; N, 5.30.

General Procedure for the Hydrazinolysis of 3-Benzoyl-5-perfluoroalkyl-1,2,4-oxadiazoles 15a−c and 3-Carboxyethyl-5-perfluoroalkyl-1,2,4-oxadiazoles 23a−c with Hydrazine or Methylhydrazine in DMF. To a mixture of the oxadiazole (1 mmol) in dry DMF (2 mL), hydrazine or methylhydrazine (3 mmol) was added. After standing 1 h at rt, the mixture was diluted with HCl 1 M and then extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated.

Reaction of 3-Benzoyl-5-trifluoromethyl-1,2,4-oxadiazole 15a with Methylhydrazine. Chromatography of the residue gave 4-trifluoroacetylamino-2-methyl-5-phenyl-2*H*-1,2,3-triazole **22a**: (64%) mp 109−111 °C (from H_2O/EtOH). ^{1}H NMR (DMSO-d_6): δ 4.28 (s, 3H), 7.44−7.57 (m, 3H), 7.72 (d, 2H, J = 7.5 Hz), 11.83 (s, 1H, exch. D_2O). ESI-MS *m/z:* 269 (M − 1, 100%, negative mode). 293 (M + Na^+, 100%, positive mode). IR (Nujol): 3240, 1716 cm^{-1}. Anal. Calcd for $C_{11}H_9N_4OF_3$: C, 48.89; H, 3.36; N, 20.73. Found: C, 48.70; H, 3.30; N, 21.70.

Reaction of 3-Benzoyl-5-heptafluoropropyl-1,2,4-oxadiazole 15b with Methylhydrazine. Chromatography of the residue gave 4-heptafluorobutanoylamino-2-methyl-5-phenyl-2*H*-1,2,3-triazole **22b**: (75%) mp 104−105 °C (from H_2O/EtOH). ^{1}H NMR (DMSO-d_6): δ 4.27 (s, 3H), 7.51−7.57 (m, 3H), 7.68 (d, 2H, J = 7.5 Hz), 11.85 (s, 1H, exch. D_2O); ESI-MS *m/z* 369 (M-1, 100%, negative mode); 393 (M+Na^+, 100%, positive mode). IR (Nujol): 3275, 1717 cm^{-1}. Anal. Calcd for $C_{13}H_9N_4OF_7$: C, 42.17; H, 2.45; N, 15.13. Found: C, 42.10; H, 2.50; N, 15.10.

Reaction of 3-Benzoyl-5-pentadecafluoroheptyl-1,2,4-oxadiazole 15c with Methylhydrazine. Chromatography of the residue gave 2-methyl-4-pentadecafluorooctanoylamino-5-phenyl-2*H*-1,2,3-triazole **22c**: (97%) mp 86−88 °C (from H_2O/EtOH). ^{1}H NMR (DMSO-d_6): δ 4.27 (s, 3H), 7.59 (q, 3H, J = 7.5 Hz), 7.67 (d, 2H, J = 7.5 Hz), 11.84 (s, 1H, exch. D_2O). ESI-MS *m/z:* 569 (M − 1, 100%, negative mode), 593 (M+Na^+, 100%, positive mode). IR (Nujol): 3283, 1713 cm^{-1}. Anal. Calcd for $C_{17}H_9N_4OF_{15}$: C, 35.81; H, 1.59; N, 9.82. Found: C, 35.80; H, 1.50; N, 10.00.

Reaction of 3-Carboxyethyl-5-trifluoromethyl-1,2,4-oxadiazole 23a with Hydrazine. Chromatography of the residue gave 1*H*-5-Hydroxylamino-3-trifluoromethyl-1,2,4-triazin-6-one **27a**: (97%) mp 202−203 °C (from H_2O/EtOH). ^{1}H NMR (DMSO-d_6): δ 10.07 (s, 1H, exch. D_2O), 11.72 (s, 1H, exch. D_2O), 12.94 (s, 1H, exch. D_2O). IR (Nujol): 3404, 3354, 3213, 1683, 1647 cm^{-1}. HRMS: calcd for $C_4H_3N_4O_2F_3$, 196.02082; found, 196.02122.

Reaction of 3-Carboxyethyl-5-heptafluoropropyl-1,2,4-oxadiazole 23b with Hydrazine. Chromatography of the residue gave 1*H*-5-hydroxylamino-3-heptafluoropropyl-1,2,4-triazin-6-one **27b**: (95%) mp 219−220 °C (from H_2O/EtOH). ^{1}H NMR (DMSO-d_6): δ 9.95 (s, 1H, exch. D_2O), 11.88 (s, 1H, exch. D_2O), 13.11 (s, 1H, exch. D_2O). IR (Nujol): 3311, 3109, 3061, 1672, 1661, 1599 cm^{-1}. HRMS: calcd for $C_6H_3N_4O_2F_7$, 296.01444; found, 296.01495.

Reaction of 3-Carboxyethyl-5-pentadecafluoroheptyl-1,2,4-oxadiazole 23c with Hydrazine. Chromatography of the residue gave 1*H*-5-hydroxylamino-3-pentadecafluoroheptyl-1,2,4-triazin-6-one **27c**: (90%) mp 221−222 °C (from H_2O/EtOH). ^{1}H NMR (599.7 MHz, DMSO-d_6, 25 °C): δ 9.89 (bs, 1H), 11.83 (bs, 1H), 13.03 (bs,1H). ^{13}C NMR (150.8 MHz, DMSO-d_6, 25 °C, ^{1}H decoupled): δ 141.5 (bs, Cq), 149.6 (bs, Cq), 153.2 (bs, Cq). ^{13}C NMR (150.8 MHz DMSO-d_6, 25 °C, ^{19}F decoupled): δ 108.3, 110.2, 110.8, 111.1 (2 signals), 111.9, 117.1 (CF_3). ^{19}F NMR (564.2 MHz, DMSO-d_6, 25 °C): δ −126.2, −122.9, −122.2. −121.7, −121.6,

−114.0, −80.7 (CF_3). IR (Nujol): 3319, 3138, 3061, 1672, 1661, 1599 cm^{-1}. HRMS: calcd for $C_{10}H_3N_4O_2F_{15}$, 496.00167; found, 496.00171.

Reaction of 3-Carboxyethyl-5-trifluoromethyl-1,2,4-oxadiazole 23a with Methylhydrazine. Chromatography of the residue gave 1-*N*-methyl-5-hydroxylamino-3-trifluoromethyl-1,2,4-triazin-6-one **28a**: (81%) mp 185−186 °C (from H_2O/EtOH). ^1H NMR (DMSO-d_6): δ 3.57 (s, 3H), 10.02 (s, 1H, exch. D_2O), 11.91 (s, 1H, exch. D_2O). IR (Nujol): 3213, 3088, 1674, 1631 cm^{-1}. HRMS: calcd for $C_5H_5N_4O_2F_3$, 210.03647; found, 210.03640.

Reaction of 3-Carboxyethyl-5-heptafluoropropyl-1,2,4-oxadiazole 23b with Methylhydrazine. Chromatography of the residue gave 1-*N*-methyl-5-hydroxylamino-3-heptafluoropropyl-1,2,4-triazin-6-one **28b**: (96%), mp 99−100 °C (from H_2O/EtOH). ^1H NMR (DMSO-d_6): δ 3.60 (s, 3H), 10.01 (s, 1H, exch. D_2O), 11.93 (s, 1H, exch. D_2O). IR (Nujol) 3234, 3188, 1654, 1637, 1605 cm^{-1}. HRMS: calcd for $C_7H_5N_4O_2F_7$, 310.03008; found, 310.03028.

Reaction of 3-Carboxyethyl-5-pentadecafluoroheptyl-1,2,4-oxadiazole 23c with Methylhydrazine. Chromatography of the residue gave 1-*N*-methyl-5-hydroxylamino-3-pentadecafluoroheptyl-1,2,4-triazin-6-one **28c**: (94%), mp 140−141 °C (from H_2O/EtOH). IR (Nujol): 3396, 3265, 1693, 1657, 1637 cm^{-1}. ^1H NMR (599.7 MHz, DMSO-d_6, 25 °C): δ 3.55 (s, 3H), 9.95 (bs, 1H), 11.85 (bs, 1H). ^{13}C NMR (150.8 MHz, DMSO-d_6, 25 °C, ^1H decoupled): δ 38.2 (Me), 140.4 (t, J_{C-F} = 25.0 Hz, Cq), 148.2 (Cq), 152.0 (Cq). ^{13}C NMR (150.8 MHz, DMSO-d_6, 25 °C, ^{19}F decoupled): δ 107.9, 109.7, 110.3, 110.6, 110.7, 111.4, 116.6 (CF_3). ^{19}F NMR (564.2 MHz, DMSO-d_6, 25 °C): δ −126.1, −122.7, −122.0. −121.4, −121.1, −113.8, −80.7 (CF_3). ^{15}N NMR (60.8 MHz, DMSO-d_6, 25 °C): δ 159.6, 185.4, 205.1, 275.2. HRMS: calcd for $C_{11}H_5N_4O_2F_{15}$, 510.01732; found, 510.01729.

Benzoylation of the 1*H*-5-Hydroxylamino-3-heptafluoropropyl-1,2,4-triazin-6-one 27b. To a mixture of **27b** (296 mg, 1 mmol) in benzene (20 mL), pyridine (0.1 mL) was added under stirring at room temperature. After dissolution, benzoyl chloride (0.255 mL, 2.2 mmol) was added, and the stirring continued for 24 h at rt. After removal of the solvent at reduced pressure, the residue was treated with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated. Crystallization of the residue from EtOH/water gave *O*,*N*-dibenzoyl-5-hydroxylamino-3-heptafluoropropyl-1,2,4-triazin-6-one (**30**): (91%) mp 185−186 °C (from H_2O/EtOH). ^1H NMR (599.7 MHz, DMSO-d_6, 25 °C): δ 7.52 (t, 2H, J = 7.6 Hz), 7.59 (t, 2H, J = 7.7 Hz), 7.64 (t, 1H, J = 7.6 Hz), 7.71 (t, 1H, J = 7.7 Hz), 7.88 (t, 2H, J = 7.6 Hz), 8.02 (t, 2H, J = 7.7 Hz), 14.40 (bs, 1H). ^{13}C NMR (150.8 MHz, DMSO-d_6, 25 °C, ^1H decoupled): δ 107.9 (ttq, $^1J_{C-F}$=269.8, $^2J_{C-F}$ = 36.8 and 32.3 Hz, CF_2), 110.2 (tt, $^1J_{C-F}$ = 258.2, $^2J_{C-F}$ = 32.3 Hz, CF_2), 117.1 (qt, $^1J_{C-F}$ = 292.8, $^2J_{C-F}$ = 36.8 Hz, CF_3), 125.1 (Cq), 128.9 (2CH), 129.0 (2CH), 129.2 (2CH), 129.8 (2CH), 131.5 (Cq), 133.7 (CH), 135.1 (CH), 137.3 (t, $^2J_{C-F}$ = 26.1 Hz, Cq), 149.1 (Cq), 156.1 (Cq), 163.6 (CO), 166.9 (CO). ^{19}F NMR (564.2 MHz, DMSO-d_6, 25 °C): δ −126.9, −115.7, −80.6 (CF_3). ^{15}N NMR (60.8 MHz, DMSO-d_6, 25 °C): δ 187.8, 207.7, 263.2, 305.3. IR (Nujol): 3172, 3070, 1770, 1738, 1693 cm^{-1}. HRMS: calcd for $C_{20}H_{11}F_7N_4O_4$, 504.06685; found, 504.06673.

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Supporting Information Available: General experimental details; crystallographic data, and ORTEP drawings of compounds **9c**, **28c**, and **30**; ^1H ^{13}C g-HMBC spectra for compounds **9a** and **14a**; geometry comparison between the X-ray derived structure of **28c** and **30**; the calculated structure of **28a**; and ab initio optimized geometry and GIAO chemical shift calculations for the three tautomers of **28a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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