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Fluorinated heterocyclic compounds. A photochemical synthesis of 3-amino-5-perfluoroaryl-1,2,4-oxadiazoles

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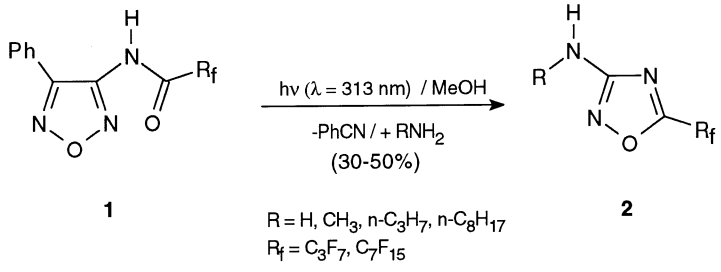
Abstract—A photochemical methodology for the synthesis of 3-amino- (or 3-*N*-substituted amino) 5-pentafluorophenyl-1,2,4-oxadiazoles is reported. Irradiation of 3-pentafluorobenzoylamino-4-methyl-1,2,5-oxadiazole (Furazan) at 254 nm in methanol and in the presence of ammonia, primary or secondary aliphatic amines produces 3-amino-, 3-(*N*-alkylamino)-, 3-(*N*,*N*-dialkylamino)-5-pentafluorophenyl-1,2,4-oxadiazoles. The photoreaction follows the fragmentation pattern of the furazan ring with the extrusion of acetonitrile and the formation of a counterpart fragment which the nitrogen nucleophile will capture. Depending on the nature of the reagent, displacement of a fluoride anion at the C(5)-pentafluorophenyl moiety of the first-formed oxadiazoles by the nitrogen nucleophile and/or the solvent also takes place. By the same photochemical approach, the synthesis of the 3-methoxy-5-pentafluorophenyl-1,2,4-oxadiazole is also described. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

A growing interest in fluorinated heterocycles owing to their applications in industrial or pharmaceutical areas currently prompts development of new synthetic methodologies for targeted compounds.[1] Alongside the direct fluorination or perfluoroalkylation reactions, widely applicable approaches to fluorinated heterocycles exploit modifications of fluorinated precursors, or the construction of the targeted structure by using fluorinated fragments in cycloadditions or cyclocondensations.[1] A very promising methodology can also be recognized in the ring-rearrangement reactions of suitable fluorinated heterocycles, and among these reactions, a very *soft* strategy would be photoinduced rearrangements of O–N bond containing azoles.[2]

In the context of our research dealing with fluorinated five-membered heterocycles, we became interested in the synthesis of 1,2,4-oxadiazoles bearing at C(3) a functional group which can confer specific properties on the fluorinated molecule. In this connection, it appears worthwhile to note that 1,2,4-oxadiazoles have been receiving great attention in the pharmaceutical industry.[3,4] In fact, oxadiazoles have been described as peptidomimetics,[3] or as bioisosteres for amides and esters,[4] and some 3-amino derivatives have been found to act as potent and efficacious muscarinic agonists.[4a,b] In this context we recently reported[5] a photochemical approach to 3-amino-, and 3-(*N*-alkylamino)-5-perfluoroalkyl-1,2,4-oxadiazoles (**2**) by photolysis of 3-perfluoroalkanoylamino-4-phenyl-1,2,5-oxadiazoles (furazans) (**1**) at 313 nm in methanol and in the presence of nitrogen nucleophiles such as ammonia, or



1

R = H, CH_3, n-C_3H_7, n-C_8H_{17}
R_f = C_3F_7, C_7F_{15}

2

Scheme 1.

Keywords: fluorinated aminooxadiazoles; pentafluorobenzoylaminofurazans; photochemistry; perfluoroaryloxadiazoles.

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primary aliphatic amines (Scheme 1). This photoreaction, which had been previously reported for non-fluorinated systems,[6] is explained by assuming a photoinduced ring fragmentation[2a,b] into benzonitrile and a nitriloxide species that the nucleophilic reagent will capture to give an *N*-acylaminoamidoxime intermediate as a precursor of the final product. Unlike non-fluorinated 5-alkyl-1,2,4-oxadiazoles, 5-perfluoroalkyl compounds **2** showed some photoreactivity, thus suggesting irradiation at low conversion of starting material. For these reasons, yields of the isolated oxadiazoles **2** were not excellent; however, this photochemical methodology has advantages when compared with the troublesome non-photochemical procedures.

In order to extend this photochemical methodology to the synthesis of different fluorinated oxadiazoles, we have now considered a similar approach for the synthesis of 5-pentafluorophenyl-1,2,4-oxadiazoles bearing an amino, *N*-alkylamino, or *N*,*N*-dialkylamino group at the C(3) of the ring. Conventional methodologies[7] for the synthesis of these fluoro-substituted compounds would present some difficulties. In fact, 3-aminooxadiazoles (but not their *N*-substituted derivatives) are generally obtained by the reaction of *N*-acylcyanamides with hydroxylamine followed by heterocyclization of resulting intermediates.[8] Other methods (which have been also used for the preparation of *N*-substituted derivatives) include the reaction of *N*-aroyl-*S*-methylisothioureas[9] with hydroxylamine, oxidative cyclization of *N*-acylguanidines[10] and the reaction of *N*-hydroxyguanidine with acylating reagents in an acylation/cyclodehydration pattern.[4a–c] In some instances,[11,12] 3-(*N*-substituted amino)oxadiazoles have been obtained from the corresponding 3-halo compounds by nucleophilic displacement of the halide ion with primary or secondary aliphatic amines. To realize our aim, we then looked at the photolysis of 3-pentafluorobenzoylamino compound **4** irradiated in the presence of ammonia, primary or secondary aliphatic amines, relying on the regiochemistry of the furazan ring breaking (which involves the O(1)–N(5) bond and extrusion of acetonitrile) already observed[2b,12] for unfluorinated analogues.

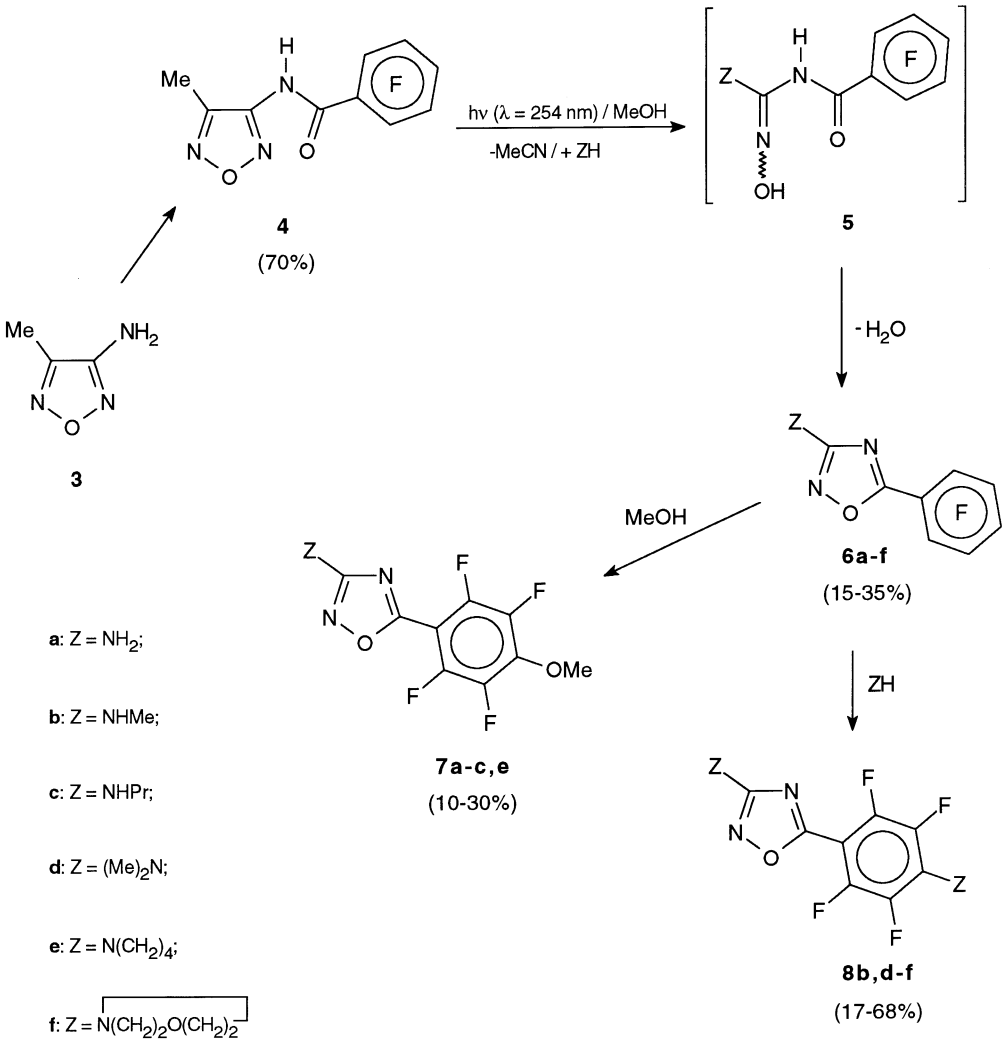
2. Results and discussion

Irradiations of the furazan **4**, which was easily obtained by pentafluorobenzoylation of the 3-amino compound **3**,[13] were carried out at 254 nm in methanol and in the presence of a slight excess of the nitrogen nucleophile. This choice was a compromise to avoid competing reactions with the nucleophilic solvent on one hand, and to minimize base-promoted hydrolysis of intermediates, on the other. Moreover, because of the expected photoreactivity of the final oxadiazoles under experimental conditions, irradiations have not been run for long times. For these reasons, depending on the reagent used, photochemical experiments were carried out in different conditions so as to have efficient synthetic results. Note that, differently from 4-phenyl substituted furazans **1** (which were irradiated at 313 nm), irradiations of the 4-methyl substituted furazan **4** were carried out at 254 nm, and this is because of different chromophores in the two furazan systems.

Irradiations of compound **4** in the presence of a large excess of methanolic ammonia allowed us to isolate both the 3-amino-5-pentafluorophenyl-1,2,4-oxadiazole (**6a**) and the 5-(2,3,5,6-tetrafluoro-4-methoxyphenyl)- derivative **7a** in different ratios depending on the work-up procedure (Scheme 2). In a typical experiment, allowing the photolysate to stand for 24 h in the dark, **6a** and **7a** were isolated in 15 and 25% yields, respectively. Some minor products were present; among these, significative amounts of the pentafluorobenzamide (likely arising from ammonolysis of open-chain intermediates) were obtained. Monitoring the photoreaction by TLC analyses, we observed that soon after the irradiation only trace amounts of final products **6a** and **7a** were present, whereas a significant species (likely the supposed *N*-acylaminoamidoxime **5a**) was detected. (A quick work-up procedure of the photolysate performed immediately after irradiation allowed us to isolate **5a**, which, if kept in methanolic triethylamine, slowly gave **6a** and **7a** together with other by-products.) On the other hand, when the photolysate was allowed to stand for more than 24 h, yields of **6a** decreased, whereas yields of **7a** increased. Consequently, the formation of the latter in the photoreaction can be explained by assuming a base-assisted solvolysis taking place at the C(5)-pentafluorophenyl ring of the initially formed **6a**, and this hypothesis was also confirmed by a separate reaction of **6a** with methanolic triethylamine. Solvolytic displacement of a fluoride anion in **6a** leading to **7a** is activated by the electron-deficient oxadiazole heterocycle, as similar nucleophilic displacement of fluoride does not take place in the pentafluorobenzoylamino compound **4**. When we tried to prepare the 3-aminooxadiazole **6a** by non-photochemical methodology, we found that attempts to achieve **6a** by the acylcyanamide route were unsuccessful. On the other hand, the pentafluorobenzoylation/cyclodehydration route of *N*-hydroxyguanidine allowed us to obtain **6a** in very low overall yields.[14]

We next examined irradiations of compound **4** in the presence of methylamine and propylamine as representative primary aliphatic amines. Irradiation of **4** in the presence of methylamine and work-up of the photolysate after 24 h gave **7b** and **8b**. On the other hand, by working up the photolysate soon after irradiation the expected **6b**, **7b** and **8b** were isolated. In turn, irradiations in the presence of propylamine gave **6c** and **7c**, whereas **8c** was not detected. Again, oxadiazoles **7b**,**c** and **8b** originate from solvolysis or aminolysis of the first formed oxadiazoles **6b**,**c** (Scheme 2).

As for secondary amines, we studied irradiations in the presence of dimethylamine, pyrrolidine and morpholine. In a typical experiment, irradiation of **4** in the presence of dimethylamine, and work-up of the photolysate soon after irradiation, gave the expected 3-dimethylamino-5-pentafluorophenyl-1,2,4-oxadiazole (**6d**) (24%) and the corresponding *p*-dimethylamino substituted compound **8d** (45%). In turn, when the photolysate was worked up after standing 24 h, no oxadiazole **6d** was isolated, whereas compound **8d** was formed in about 68% yield. A similar result was observed in the irradiation of **4** in the presence of pyrrolidine: depending on the work-up procedure, mixtures of compounds **6e**, **7e** and **8e**, on one hand, or compounds **7e** and **8e**, on the other, were obtained. Isolation



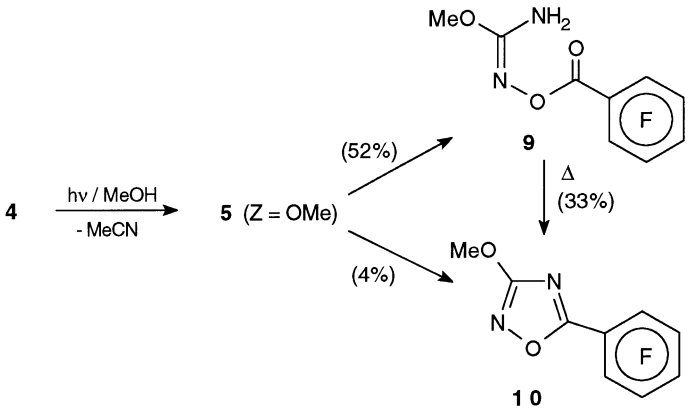
Scheme 2.

of the oxadiazole **6e** (in about 28% yield) was realized by neutralization of the photolysate with hydrochloric acid soon after the irradiation, followed by column chromatography. Furthermore, irradiations of **4** in the presence of morpholine, gave the 3-*N*-morpholinyl oxadiazole **6f** (35%) and the *p*-substituted compound **8f** (17%).

As for the structure of substituted compounds **7** and **8**, ^{19}F NMR analyses unequivocally proved the entry of the oxygen or nitrogen nucleophiles in the *para* position of the pentafluorophenyl ring. Two doublets with a coupling constant of ca 20 Hz were present in the spectra of all compounds, as expected for the presence of two *ortho* positioned pairs of fluorine atoms, but with line broadening or further few Hz splittings of these doublets resulting from the *para* and *meta* couplings.[15] Comparison with similarly substituted tetrafluorophenyl ring[16] allowed the upper and lower field doublets (in the ranges −153.2/−162.9 and −138.1/−140.1 ppm, respectively) to be assigned to the fluorine atoms *ortho* and *meta* to the entering nucleophile, respectively. At this stage we have not studied the influence of different parameters involved in the formation of these substituted compounds, or the competition between solvolysis and aminolysis reactions.

To verify the possibility of exploiting this photochemical approach for the synthesis of the 3-methoxy-5-pentafluorophenyloxadiazole (**10**), we then examined photolysis of the furazan **4** in methanol only, relying on the nucleophilic character of the solvent. (This behavior had been already pointed out for non-fluorinated analogues.[2b]) This irradiation gave a mixture of components from which, after standing of the photolysate for 24 h, we isolated the *O*-acylamidoxime **9** [(50%); likely arising from the corresponding *N*-acylamidoxime (**5**; Z=OMe), or from a carbodiimide species; see unfluorinated analogues[2b]], but a few percent of the oxadiazole **10** (Scheme 3). Low yields of the oxadiazole component could be due to the competing development of open-chain intermediates. On the other hand, subsequent photoreactivity of the first-formed 3-methoxyoxadiazole **10** under the reaction conditions could also play a role. (A complete study on photoreactivities of fluorinated 1,2,4-oxadiazoles will follow.) Nevertheless, the oxadiazole **10** was efficiently obtained by thermal cyclodehydration of **9**.

In conclusion, all the results described in this paper, together with those previously reported,[5] show that this unprecedented photochemical approach[17] appears as an efficient



Scheme 3.

methodology for the synthesis of 1,2,4-oxadiazoles bearing a perfluorinated aryl moiety at C(5) and an amino, *N*-alkylamino, *N*,*N*-dialkylamino or a methoxy group at C(3). Although yields were not excellent (they could be improved by optimizing experimental conditions), these results appear to be of some significance in view of troublesome non-photochemical procedures for the synthesis of these compounds. Moreover, they open new synthetic strategies toward targeted fluorinated structures, by exploiting photo-induced rearrangements of suitable fluorinated heterocyclic precursors.

3. Experimental

3.1. Material and methods

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra (Nujol) were determined with a Perkin–Elmer 257 instrument, ^{1}H NMR spectra were recorded on a Bruker 250 E spectrometer, and ^{19}F NMR on a Bruker AV 500 instrument (bd stands for broad doublet). GC/MS determinations were carried out by using a VARIAN STAR 3400 CX/SATURN 2000 system. Flash chromatography was performed by using mixtures of ethyl acetate and light petroleum (fraction boiling in the range of 40–60°C) in varying ratios. Freshly prepared saturated methanolic ammonia, ethanolic (33%) methylamine and dimethylamine (Fluka), propylamine (Aldrich), and freshly distilled pyrrolidine or morpholine (Aldrich) were used. Photochemical reactions were carried out in anhydrous methanol (Romil Co.) in quartz vessels, by using a Rayonet RPR-100 photoreactor, equipped with 16 Hg-lamps irradiating at 254 nm (RPR-2537°) and a merry-go-round apparatus.

3.1.1. 3-Pentafluorobenzoylamino-4-methylfurazan (4). Compound **4** was prepared by reacting 3-amino-4-methylfurazan (**3**)[13] (3 g, 30 mmol) with pentafluorobenzoyl chloride (7.6 g, 33 mmol) in anhydrous benzene (100 mL) containing pyridine (2.7 mL, 33 mmol). Addition of the acyl chloride (diluted in 50 mL of anhydrous benzene) was made slowly and with stirring, and then the mixture was left at room temperature for 24 h. After removal of the solvent under reduced pressure, the residue was worked-up with water and then filtered. The crude mixture was purified by chromatography and then by crystallization from benzene containing light petroleum. Yield 70%; mp 184–186°C. IR: 3240, 3200, 3180, 3095, 1690 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.83 (s, 3H), 12.39 (s, 1H). MS *m*/*z*: 293 (2) (M^+), 250 (11), 195 (100), 167 (13), 117 (30), 93 (4). Anal. Calcd for $C_{10}H_4F_5N_3O_2$: C, 40.97; H, 1.38; N, 14.33. Found: C, 41.10; H, 1.50; N, 14.45.

3.2. General procedure for irradiation of compound 4 in the presence of nitrogen nucleophiles

To a solution of compound **4** (0.5 g; 1.7 mmol) in anhydrous methanol (300 mL) the appropriate nitrogen nucleophile was added [i.e. methanolic ammonia (5 mL; 30 mmol), methanolic methylamine (1.1 mL; 8.5 mmol), propylamine (0.7 mL; 8.5 mmol), methanolic dimethylamine (1.5 mL; 8.5 mmol), pyrrolidine (0.7 mL; 8.5 mmol), and morpholine (0.75 mL; 8.5 mmol)]. The mixture was apportioned into six quartz tubes and then irradiated for 1.5 h. The photolysates were then worked up as reported below. After removal of the solvent under reduced pressure at room temperature, the residue was chromatographed. Amounts of untractable materials or minor components were discarded.

3.2.1. Irradiation of compound 4 in the presence of ammonia. The photolysate was left to stand for 24 h in the dark. Chromatography of the residue returned starting material (0.1 g; 20%), and gave the 3-amino-5-pentafluorophenyl-1,2,4-oxadiazole (**6a**) (0.064 g; 15%), the 3-amino-5-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-1,2,4-oxadiazole (**7a**) (0.11 g; 25%), and then some amounts of pentafluorobenzamide (0.036 g; 10%), mp 146–147°C.

Compound **6a** had mp 174–175°C (from light petroleum). IR: 3400, 3330, 3240 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 6.76 (s). MS *m*/*z*: 251 (79) (M^+), 194 (35), 117 (59), 93 (21), 58 (100). Anal. Calcd for $C_8H_2F_5N_3O$: C, 38.26; H, 0.8; N, 16.73. Found: C, 38.40; H, 1.0; N, 16.90.

Compound **7a** had mp 192–193°C (from light petroleum). IR: 3380, 3320, 3230 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 4.25 (s, 3H), 6.69 (s, 2H). ^{19}F NMR ($CDCl_3$): δ −138.10 (bd, 2F, J=20.8 Hz), −157.84 (bd, 2F, J=19.5 Hz). MS *m*/*z*: 263 (90) (M^+), 206 (100), 163 (11), 117 (25), 58 (31). Anal. Calcd for $C_9H_5F_4N_3O_2$: C, 41.08; H, 1.92; N, 15.97. Found: C, 41.20; H, 2.0; N, 16.10.

In a further experiment, a sample of **4** (0.25 g) in methanol (150 mL) containing methanolic ammonia (4 mL) apportioned in three tubes was irradiated for 1 h and then the solvent was removed soon after the irradiation. A quick chromatography, after discarding first fractions containing mixtures of the starting material and oxadiazole components (see before), gave almost pure **5a** (0.1 g; 43%); mp 93–98°C (dec). IR: 3480, 3340, 3250, 1720 cm^{-1}. ^1H NMR (DMSO-d_6): δ: 7.43 (br s, 2H), 9.48 and 10.84 (2s, 2H). A sample of **5a** in methanolic triethylamine at room temperature slowly gave **6a** and **7a** (by HPLC and GC–MS).

A sample of **6a** was obtained by reacting equimolar amounts of *N*-hydroxyguanidine (crude free base freshly prepared from *S*-methylisothiourea and hydroxylamine)[18] with pentafluorobenzoyl chloride. In our hands, the usual work-up procedure allowed to isolate **6a** in very low yields.[14]

3.2.2. Irradiation of compound 4 in the presence of methylamine. The photolysate was left to stand for 24 h. Chromatography of the residue returned starting material (0.1 g; 20%), and gave at first the 3-(*N*-methylamino)-5-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-1,2,4-oxadiazole (**7b**) (0.14 g; 30%) and then the 3-(*N*-methylamino)-5-(2,3,5,6-tetrafluoro-4-*N*-methylaminophenyl)-1,2,4-oxadiazole (**8b**) (0.14 g; 30%).

Compound **7b** had mp 132–133°C (from light petroleum). IR: 3340 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.81 (d, 3H, J=4.8 Hz), 4.25 (s, 3H), 7.20 (q, 1H, J=4.8 Hz). ^{19}F NMR ($CDCl_3$): δ −138.29 (bd, 2F, J=20.8 Hz), −157.95 (bd, 2F, J=20.0 Hz). MS *m/z*: 277 (42) (M^+), 207 (39), 117 (22), 72 (41), 42 (100). Anal. Calcd for $C_{10}H_7F_4N_3O_2$: C, 43.33; H, 2.55; N, 15.16. Found: C, 43.40; H, 2.70; N, 15.30.

Compound **8b** had mp 192–194°C (from light petroleum). IR: 3320 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.78 (d, 3H, J=5.0 Hz), 3.11 (d, 3H, J=3.0 Hz), 6.9–7.1 (m, 2H). ^{19}F NMR ($CDCl_3$): δ −139.80 (bd, 2F, J=19.4 Hz), −162.92 (bd, 2F, J=22.0 Hz). MS *m/z*: 276 (100) (M^+), 206 (59), 178 (10), 138 (18), 117 (14), 83 (42), 42 (87). Anal. Calcd for $C_{10}H_8F_4N_4O$: C, 43.49; H, 2.92; N, 20.29. Found: C, 43.40; H, 2.90; N, 20.20.

In a further experiment, the solvent was removed soon after the irradiation. Chromatography of the residue gave, besides starting material (0.1 g; 20%), gave 3-(*N*-methylamino)-5-pentafluorophenyl-1,2,4-oxadiazole (**6b**) (0.08 g; 18%) and then **7b** (0.05 g; 10%) and **8b** (0.10 g; 20%).

Compound **6b** had mp 89–92°C (from light petroleum). IR: 3280 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.83 (d, 3H, J=5.0 Hz), 7.26 (q, 1H, J=5.0 Hz). MS *m/z*: 265 (54) (M^+), 195 (56), 167 (7), 117 (42), 93 (12), 72 (38), 42 (100). Anal. Calcd for $C_9H_4F_5N_3O$: C, 40.77; H, 1.52; N, 15.85. Found: C, 40.70; H, 1.60; N, 16.0.

3.2.3. Irradiation of compound 4 in the presence of propylamine. The photolysate was left to stand for 12 h. Chromatography of the residue returned starting material (0.1 g; 20%), and gave 3-(*N*-propylamino)-5-pentafluorophenyl-1,2,4-oxadiazole (**6c**) (0.15 g; 25%), and 3-(*N*-propylamino)-5-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-1,2,4-oxadiazole (**7c**) (0.16 g; 30%).

Compound **6c** had mp 48–49°C (from light petroleum). IR: 3320 cm^{-1}. ^1H NMR (DMSO-d_6): δ 0.96 (t, 3H, J=7.4 Hz), 1.61 (m, 2H), 3.14 (m, 2H), 7.39 (t, 1H, J=5.7 Hz). MS *m/z*: 293 (10) (M^+), 264 (100), 195 (82), 167 (26), 117 (51). Anal. Calcd for $C_{11}H_8F_5N_3O$: C, 45.06; H, 2.75; N, 14.33. Found: C, 45.20; H, 2.90; N, 14.50.

Compound **7c** had mp 78–80°C (from light petroleum). IR: 3290 cm^{-1}. ^1H NMR (DMSO-d_6): δ 0.99 (t, 3H, J=7.4 Hz), 1.61 (m, 2H) 3.14 (m, 2H), 4.25 (s, 3H), 7.39 (t, 1H, J=5.7 Hz). ^{19}F NMR ($CDCl_3$): δ −138.27 (bd, 2F, J=22.1 Hz), −157.85 (bd, 2F, J=19.3 Hz). MS *m/z*: 305 (7) (M^+), 276 (41), 207 (100), 163 (9), 117 (15). Anal. Calcd for $C_{12}H_{11}F_4N_3O_2$: C, 47.22; H, 3.63; N, 13.77. Found: C, 47.30; H, 3.70; N, 13.90.

3.2.4. Irradiation of compound 4 in the presence of dimethylamine. The photolysate was left to stand for 12 h. Chromatography of the residue returned starting material (0.075 g; 15%), and gave 3-(*N*,*N*-dimethylamino)-5-(2,3,5,6-tetrafluoro-4-*N*,*N*-dimethylaminophenyl)-1,2,4-oxadiazole (**8d**) (0.35 g; 68%).

Compound **8d** had mp 73–74°C (from light petroleum). ^1H NMR (DMSO-d_6): δ 3.03 and 3.11 (2s, 12H). ^{19}F NMR ($CDCl_3$): δ −139.48 (bd, 2F, J=19.4 Hz), −153.23 (bd, 2F, J=18.8 Hz). MS *m/z*: 304 (57) (M^+), 220 (100), 192 (17), 152 (7), 117 (4). Anal. Calcd for $C_{12}H_{12}F_4N_4O$: C, 47.37; H, 3.98; N, 18.41. Found: C, 47.5 0; H, 3.90; N, 18.50.

In a further experiment, the solvent was removed soon after the irradiation. Chromatography of the residue, besides starting material (0.075 g; 15%), gave 3-(*N*,*N*-dimethylamino)-5-pentafluorophenyl-1,2,4-oxadiazole (**6d**) (0.11 g; 24%) and then **8d** (0.23 g; 45%).

Compound **6d** had mp 53–54°C (from light petroleum). ^1H NMR ($CDCl_3$): δ 3.09 (s). MS *m/z*: 279 (68) (M^+), 195 (28), 167 (4), 117 (35), 42 (100). Anal. Calcd for $C_{10}H_6F_5N_3O$: C, 43.02; H, 2.17; N, 15.05. Found: C, 43.10; H, 2.30; N, 15.20).

3.2.5. Irradiation of compound 4 in the presence of pyrrolidine. The photolysate was left to stand for 12 h. Chromatography of the residue returned starting material (0.075 g; 15%), and gave 3-(*N*-pyrrolidinyl)-5-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-1,2,4-oxadiazole (**7e**) (0.054 g; 10%), and then 3-(*N*-pyrrolidinyl)-5-(2,3,5,6-tetrafluoro-4-*N*-pyrrolidinylphenyl)-1,2,4-oxadiazole (**8e**) (0.36 g; 60%).

Compound **7e** had mp 75–78°C (from light petroleum). ^1H NMR ($CDCl_3$): δ 1.95–2.04 (m, 4H), 3.48–3.54 (m, 4H), 4.20 (s, 3H). MS *m/z*: 317 (44) (M^+), 250 (7), 207 (100), 162 (6),117 (25). Anal. Calcd for $C_{13}H_{11}F_4N_3O_2$: C, 49.22; H, 3.49; N, 13.25. Found: C, 49.30; H, 3.60; N, 13.40).

Compound **8e** had mp 161–163°C (from light petroleum). ^1H NMR ($CDCl_3$): δ 1.92–2.05 (m, 8H), 3.48–3.53 (m, 4H), 3.68–3.76 (m, 4H). ^{19}F NMR ($CDCl_3$): δ −140.06 (bd, 2F,

J=20.8 Hz), −157.78 (bd, 2F, J=20.8 Hz). MS m/z: 356 (100) (M^+), 287 (16), 246 (56), 176 (16), 149 (7). Anal. Calcd for $C_{16}H_{16}F_4N_4O$: C, 53.93; H, 4.53; N, 15.72. Found: C, 53.80; H, 4.40; N, 15.80.

In a further experiment, soon after the irradiation the photolysate was neutralized with few drops of hydrochloric acid and then the solvent was removed. Chromatography of the residue returned starting material (0.05 g; 10%), and gave 3-(*N*-pyrrolidinyl)-5-pentafluorophenyl-1,2,4-oxadiazole (**6e**) (0.15 g; 28%), **7e** (0.08 g; 15%) and **8e** (0.24 g; 40%).

Compound **6e** had mp 85–86°C (from light petroleum). ^{1}H NMR ($CDCl_3$): δ 2.01 (t, 4H, J=7.4 Hz), 3.49 (t, 4H, J=7.4 Hz). MS m/z: 305 (85) (M^+), 287 (76), 258 (11), 195 (57), 117 (42), 68 (100). Anal. Calcd for $C_{12}H_8F_5N_3O$: C, 47.22; H, 2.64; N, 13.77. Found: C, 47.30; H, 2.50; N, 13.90.

3.2.6. Irradiation of compound 4 in the presence of morpholine. The photolysate was left to stand for 24 h, and then neutralized with hydrochloric acid. After removal of the solvent, chromatography of the residue returned starting material (0.1 g; 20%), and gave 3-(*N*-morpholinyl)-5-pentafluorophenyl-1,2,4-oxadiazole (**6f**) (0.19 g; 35%) and 3-(*N*-morpholinyl)-5-(2,3,5,6-tetrafluoro-4-*N*-morpholinylphenyl)-1,2,4-oxadiazole (**8f**) (0.11 g; 17%).

Compound **6f** had mp 80–81°C (from light petroleum). ^{1}H NMR ($CDCl_3$): δ 3.52 (t, 4H, J=4.7 Hz), 3.80 (t, 4H, J=4.7 Hz). MS m/z: 321 (17) (M^+), 306 (24), 195 (61), 149 (100), 117 (30). Anal. Calcd for $C_{12}H_8F_5N_3O_2$: C, 44.87; H, 2.51; N, 13.08. Found: C, 44.90; H, 2.50; N, 13.10.

Compound **8f** had mp 126–128°C (from light petroleum). ^{1}H NMR ($CDCl_3$): δ 3.40–3.43 (m, 4H), 3.51–3.55 (m, 4H), 3.80–3.86 (m, 8H). ^{19}F NMR ($CDCl_3$): δ −138.49 (bd, 2F, J=21.3 Hz), −157.85 (bd, 2F, J=17.8 Hz). MS m/z: 388 (88) (M^+), 374 (65), 262 (50), 204 (46), 117 (6), 86 (85), 56 (100). Anal. Calcd for $C_{16}H_{16}F_4N_4O_3$: C, 49.49; H, 4.15; N, 14.43. Found: C, 49.40; H, 4.10; N, 14.50.

3.2.7. Irradiation of compound 4 in methanol. A solution of compound **4** (0.5 g) in methanol (300 mL) was apportioned in six quartz tubes and then irradiated for 1.5 h. The photolysate was left to stand for 24 h and then the solvent was removed. Chromatography of the residue, besides some amounts of minor components (discarded), returned starting material (0.115 g; 27%), and gave 3-methoxy-5-pentafluorophenyl-1,2,4-oxadiazole (**10**) (colorless oil which solidified under freezing) (0.020 g; 4%) and then the *O*-pentafluorobenzoylamidoxime (**9**) (0.25 g; 52%).

Compound **10** had ^{1}H NMR ($CDCl_3$) δ 4.15 (s). MS m/z 266 (100) (M^+), 208 (67), 195 (86), 181 (45), 117 (38). Anal. Calcd for $C_9H_3F_5N_2O_2$: C, 40.62; H, 1.14; N, 10.53. Found: C, 40.50; H, 1.10; N, 10.40.

Compound **9** had mp 102–103°C (from light petroleum): IR 3400, 3530, 1740 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 3.75 (s, 3H), 6.64 (s, 2H). MS m/z 284 (3) (M^+), 221 (16), 195 (71), 117.(42), 44 (100). Anal. Calcd for $C_9H_5F_5N_2O_3$: C, 38.04; H, 1.77; N, 9.86. Found: C, 38.20; H,1.90; N, 9.70.

A sample of **9** (0.13 g) was kept in an oil-bath at 120°C for 6 h. Chromatography of the residue returned starting material (0.065 g; 50%) and gave **10** (0.040 g; 33%).

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