

 Open access • Journal Article • DOI:10.3987/COM-04-10059

Fluorinated Heterocyclic Compounds. A Photochemical Approach to a Synthesis of Fluorinated Quinazolin-4-ones — [Source link](#)

Silvestre Buscemi, Andrea Pace, Antonio Palumbo Piccionello, Ivana Pibiri ...+1 more authors

Published on: 01 Jul 2004 - Heterocycles (Japan Institute of Heterocyclic Chemistry)

Topics: Moiety, Triethylamine and Photoinduced electron transfer

Related papers:

- [Fluorinated heterocyclic compounds. A photochemical synthesis of 3-amino-5-perfluoroaryl-1,2,4-oxadiazoles](#)
- [Synthesis of fluorinated indazoles through ANRORC-like rearrangement of 1,2,4-oxadiazoles with hydrazine](#)
- [The new era of 1,2,4-oxadiazoles](#)
- [Fluorinated heterocyclic compounds. An expedient route to 5-perfluoroalkyl-1,2,4-triazoles via an unusual hydrazinolysis of 5-perfluoroalkyl-1,2,4-oxadiazoles: first examples of an ANRORC-like reaction in 1,2,4-oxadiazole derivatives.](#)
- [Fluorinated heterocyclic compounds: an assay on the photochemistry of some fluorinated 1-oxa-2-azoles: an expedient route to fluorinated heterocycles](#)

Share this paper:    

View more about this paper here: <https://typeset.io/papers/fluorinated-heterocyclic-compounds-a-photochemical-approach-4q656jzohu>

**FLUORINATED HETEROCYCLIC COMPOUNDS. A
PHOTOCHEMICAL APPROACH TO A SYNTHESIS OF FLUORINATED
QUINAZOLIN-4-ONES**

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

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

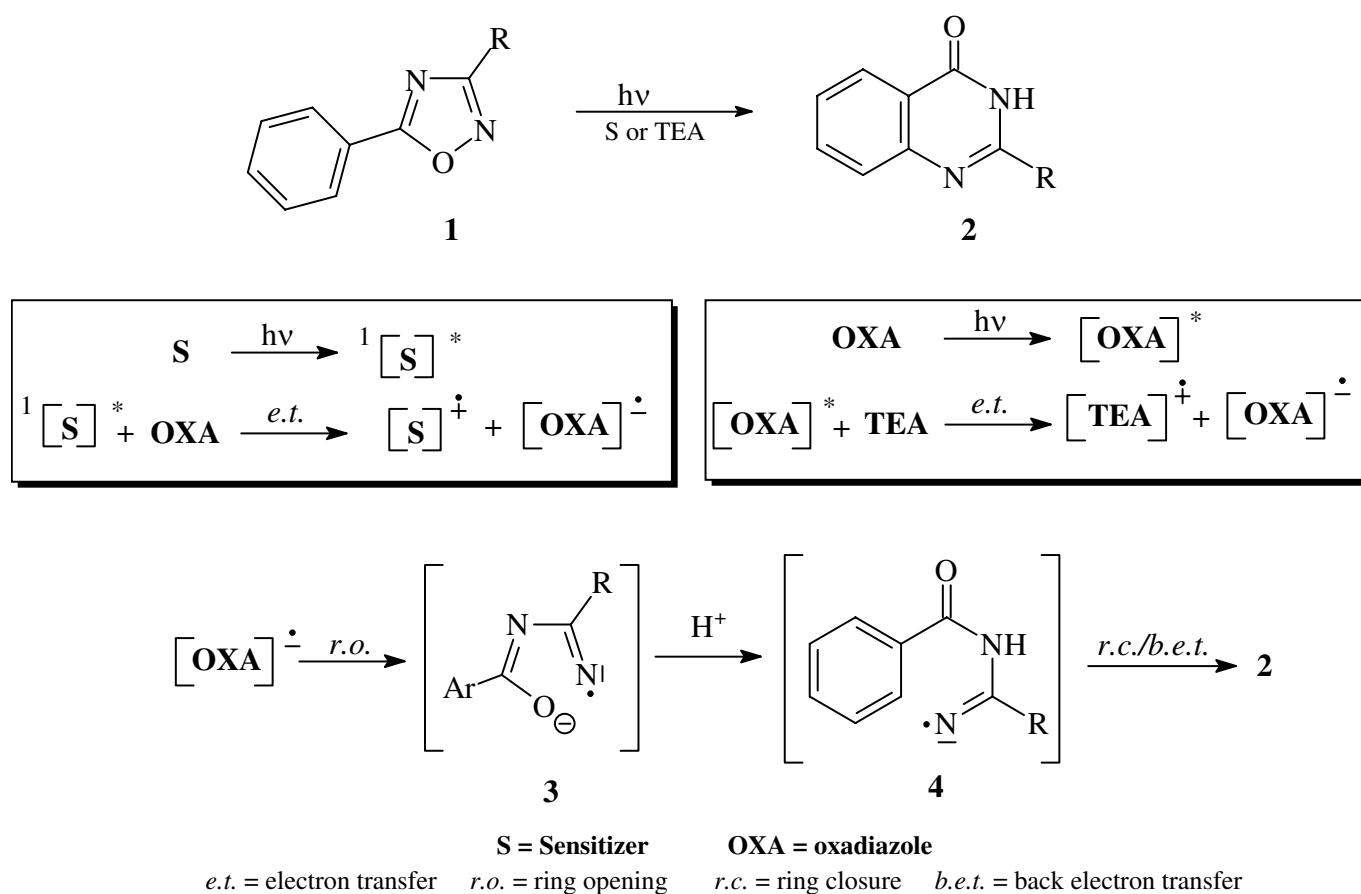
Abstract - An efficient and generalized photochemical methodology for the preparation of fluorinated quinazolin-4-ones is described. Depending on the starting substrate, quinazolin-4-ones bearing a perfluoroalkyl- or perfluoroaryl-substituent in position 2 or fluorine atoms on any positions of the benzo-fused moiety can easily be obtained. 5-Aryl-3-perfluoroalkylpentafluorophenyl- or 5-polyfluoroaryl-3-phenyl(methyl)-1,2,4-oxadiazoles, respectively, can be considered as ideal precursors that can be transformed into the target quinazolin-4-ones by irradiation in the presence of triethylamine (TEA) (at $\lambda = 313$ nm) or pyrene (at $\lambda = 365$ nm) in dry methanol or acetonitrile as solvent. Some mechanistic considerations confirm the involvement of a photoinduced electron transfer process.

INTRODUCTION

Fluorinated heterocycles are interesting compounds widely used in medicinal, agricultural and polymer chemistry, and their synthesis represents a research area of growing interest.¹ Although the direct introduction of fluorine or perfluoroalkyl groups into heterocyclic structures can be realized by using fluorinating or perfluoroalkylating reagents, a widely used approach to fluorinated heterocycles includes building-block strategies, which achieve the formation of the heterocyclic ring from fluorinated precursors.¹ In this context, a promising strategy uses the photoinduced rearrangements of O-N bond containing azoles such as furazans and 1,2,4-oxadiazoles.² In the field of photochemical strategies for the synthesis of heterocyclic compounds, an interesting reactivity of the 1,2,4-oxadiazole heterocycle is represented by the photochemical transformation of the 5-aryl-1,2,4-oxadiazole system into quinazolin-4-

ones derivatives.^{3,4} This process, which takes place under irradiation of the oxadiazoles in the presence of sensitizers or triethylamine (TEA), involves a photoinduced electron transfer between the excited sensitizer (S) (donor) and the ground state oxadiazole (OXA) (acceptor) or between the excited oxadiazole (acceptor) and the TEA (donor), followed by cyclization of the open-chain radical anion intermediate into the final quinazolin-4-one product (Scheme 1).

Scheme 1



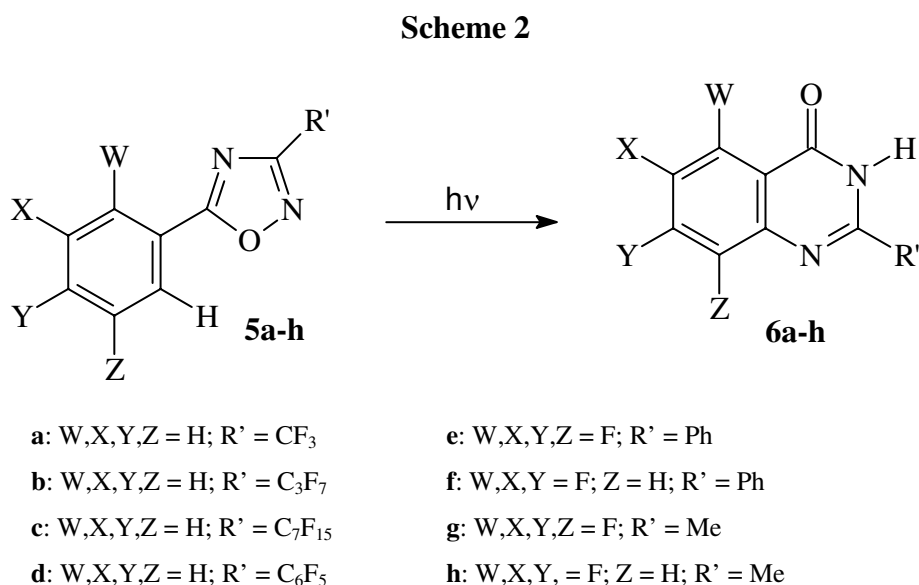
In the frame of our research^{5,6} on the synthesis of fluorinated heterocycles, we became interested in how this photoinduced process could have been applied as a general methodology for the synthesis of fluorinated quinazolin-4-ones. Our interest towards this class of compounds comes from the fact that quinazolin-4-ones are associated with a wide range of pharmaceutical properties and are used as analgesic and antiinflammatory,⁷ antimicrobial,⁸ antiparkinson,⁹ and affect the central nervous system.¹⁰ They recently have been also tested as anticancer drugs,¹¹ as anticonvulsant agents,^{12,13} and as neuropeptide Y receptor antagonists for the treatment of obesity and circulatory disorders.¹⁴ Moreover, all these properties can, in principle, be strongly affected by the presence of a fluorinated moiety.

To better introduce this work, we needed to recall that a general synthesis of the quinazolin-4-one system exploits the use of anthranilic acid fused with aliphatic amines or nitriles, in one hand, or the use of

o-aminobenzamides reacted with acylating reagents. For the synthesis of 2-perfluoroalkyl derivatives, examples of the last procedure are reported together with the use of 2-aminobenzonitrile (as a precursor) reacted with perfluoroalkanoyl chloride followed by cyclization in basic medium.¹⁵ As for our approach, we programmed the synthesis of quinazolin-4-ones bearing a fluorinated group (perfluoroalkyl- or perfluoroaryl-) at the C(2), starting from 5-aryl-1,2,4-oxadiazoles bearing the fluorinated group at the C(3). On the other hand, quinazolin-4-ones derivatives polyfluorosubstituted at the benzo-fused moiety can be obtained from the appropriate 5-polyfluoroaryl-1,2,4-oxadiazoles. The latter approach is an interesting because it allows the synthesis of fluorinated quinazolin-4-ones difficult to obtain through the above cited conventional methodologies.

RESULTS AND DISCUSSION

To realize our project, we considered two series of 1,2,4-oxadiazoles: compounds (**5a-d**) and compounds (**5e-h**) (Scheme 2). Referring to our previous results on the sensitized photorearrangement of 1,2,4-oxadiazoles, we performed irradiations in the presence of TEA (at $\lambda = 313$ nm) or in the presence of pyrene (at $\lambda = 365$ nm).



3-Perfluoroalkyloxadiazoles (**5a-c**) were prepared by an isoheterocyclic rearrangement reaction of the corresponding 5-perfluoroalkyl-3-phenyl-1,2,4-oxadiazoles with hydroxylamine in DMF.⁶ In turn, the 3-pentafluorophenyl derivative (**5d**) was obtained by the conventional procedure exploiting the reaction of the pentafluorobenzamidoxime with benzoyl chloride.¹⁶ Similarly, the 5-polyfluorophenyloxadiazoles (**5e-h**) were prepared from acetamidoxime or benzamidoxime with the appropriate polyfluorobenzoyl chloride in anhydrous toluene at reflux.¹⁷

All the photochemical reactions were performed on a preparative scale (~ 0.5 g of substrate) and were followed by chromatographic separation of the reaction mixture, where minor byproducts (< 5 %) were discarded.

Irradiations at $\lambda= 313$ nm in the presence of TEA

Considering our previous results on unfluorinated 5-aryl-1,2,4-oxadiazoles,^{3,4} we performed a series of irradiations of compounds (**5a-h**) at $\lambda = 313$ nm in the presence of TEA and using acetonitrile as solvent. Results are reported in Table 1. The use of methanol as irradiation solvent was avoided because, in the case of compounds (**5a-c**), irradiations in methanol/TEA resulted in decomposition of the intermediates, while for compounds (**5d-g**) the use of methanol causes the base-induced displacement of the 4-fluoro moiety of the aryl system with the nucleophilic solvent.^{5b} The yields are acceptable for compounds (**6d-h**), however, compounds (**6a-c**) were obtained in low yields even after a longer irradiation. The lower reactivity shown by compound (**5a-c**) could be ascribed to the very low absorbance of the substrate at the irradiation wavelength: unfortunately, alternative irradiations at $\lambda= 254$ nm were not feasible due to competing reactions of the oxadiazole substrate and photodegradation of the just formed quinazolin-4-one.

Irradiations at $\lambda= 365$ nm in the presence of pyrene

We then decided to improve our procedure trying pyrene as a sensitizer with the advantage of irradiating at a wavelength where both the substrate and the final product do not absorb, thus minimizing photodecomposition processes.

Table 1. - Yields of quinazolin-4-ones (**6a-h**) from irradiations of oxadiazoles (**5a-h**)

Compd	Irradiation with TEA ^a		Irradiation with pyrene ^b	
	Yield (%)	Recovered Starting Material	Yield (%)	Recovered Starting Material
6a	5	68 ^c	75 ^d	5
6b	5	70 ^c	40 ^d	25
6c	16	80 ^c	45 ^d	35
6d	21	69	56	25
6e	45	40	35	51
6f	35	57	35	53
6g	55	20	37	51
6h	60	10	41	54

^a Irradiation time 2 h; ^b Irradiation time 5 h; ^c Irradiation time 4 h; ^d Irradiation performed in methanol.

As shown in Table 1, irradiations of compounds (**5a-h**) in acetonitrile and in the presence of pyrene lead to the formation of quinazolin-4-ones (**6a-h**) in reasonable to good yields. [Actually, for compounds (**5a-c**) irradiations in methanol gave better results than those performed in acetonitrile where 5-10% yields were obtained together with substantial amount of unidentified decomposition byproducts]. On a separate experiment, the quinazolin-4-ones showed to be unstable under the irradiation conditions, for this reason we decided to stop the irradiation of the substrate before its complete conversion; chromatographic separation allowed to isolate the product and to recycle the unreacted starting material. It is noteworthy that this photochemical methodology allows an easy preparation of 5,6,7,8-tetrafluoro- and 5,6,7-trifluoroquinazolin-4-ones (**6e-h**) otherwise difficult to prepare by conventional procedure which should have employed polyfluoro-substituted 2-aminobenzamides (or nitriles), or polyfluoro-substituted anthranilic acid. It is interesting that, in the case of the 5-pentafluorophenylloxadiazole (**7**), the irradiation resulted in the formation of the reduction product (**9**) only; the corresponding quinazolin-4-one (**6d**) is not observed, likely because of the uneasy displacement of the 2-fluoro substituent on the aromatic ring during the cyclization step of the radical anion intermediate (**8**) (Scheme 3). Finally, considering the double nature of the pyrene as an electron-transfer and/or energy transfer sensitizer, we analyzed the singlet energies (from fluorescence emission spectra) of oxadiazoles (**5a-h**); data shown in Table 2 clearly rule out any involvement of a singlet energy transfer process between the excited pyrene ($E_S = 322 \text{ kJ mol}^{-1}$)¹⁸ and the ground state oxadiazole (with energy values of the excited state all ranging between $E_S = 408\text{-}431 \text{ kJ mol}^{-1}$) and this supports the hypothesis of a photoinduced electron transfer involved in the photoreaction mechanism and is in agreement with what previously reported for the unfluorinated analogues.³

Scheme 3

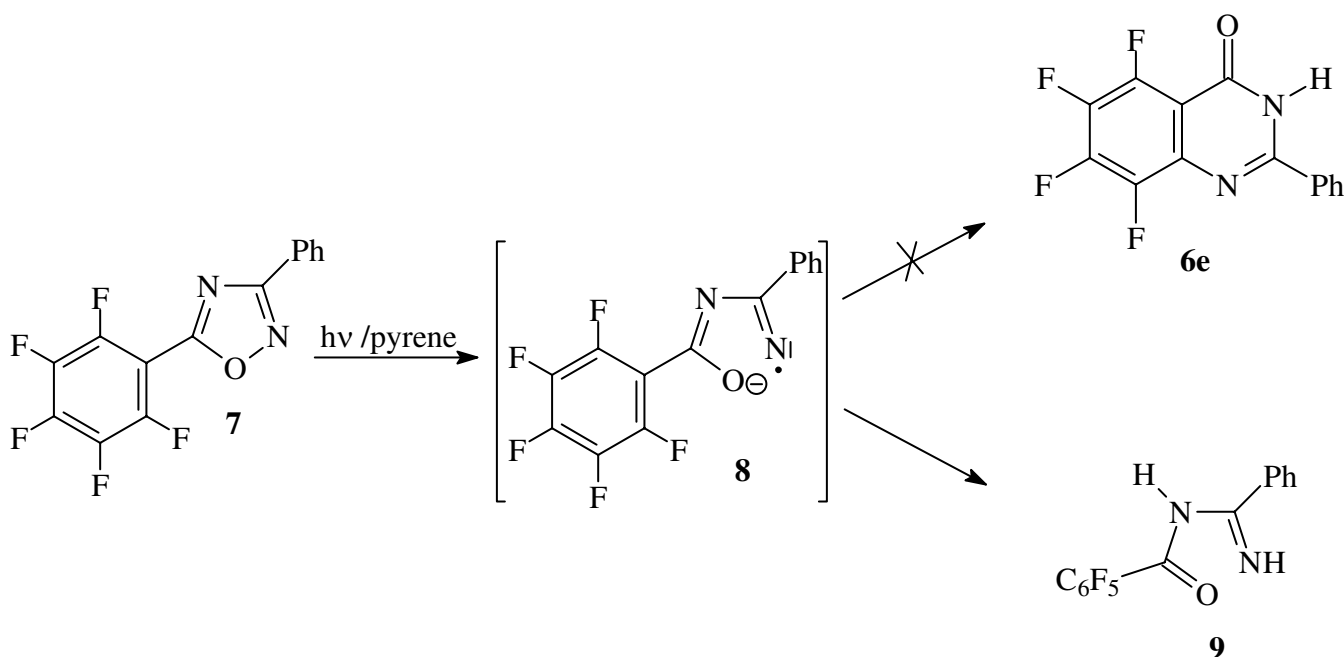


Table 2. – UV absorption (λ_{\max}) and energy values of the singlet excited state (E_s) of compounds (**5a-h**) as determined from fluorescence emission spectra in methanol

Compound	λ_{\max} (nm)	E_s (kJ/mol)
5a	253	416
5b	254	419
5c	254	420
5d	252	410
5e	243	411
5f	246	408
5g	243	409
5h	247	431

Table 3. - Physical and analytical data for quinazolin-4-ones (**6a-h**).

Compd	Mp (°C)	IR(nujol) ν (cm ⁻¹)	¹ H NMR (TMS) δ (ppm)	MS m/z (%)	Molecular Formula	Analysis Calcd (Found) C/H/ N
6a	245-248 ^a					
6b	158-160 ^b					
6c	178-180 ^c					
6d	279-281 ^d	3160, 1665	7.65-7.69 ^e (m, 1H, Ar), 7.77-7.80 (m, 1H, Ar), 7.88-7.92 (m, 1H, Ar), 8.25-8.29 (m, 1H, Ar),	312 (M ⁺ , 100), 195 (15), 124 (25), 117 (26), 90 (36), 63 (55)	C ₁₄ H ₅ N ₂ OF ₅	53.86/1.61/8.97 (53.80/1.50/8.80)
6e	312-313 ^d	3172, 1680	7.63-7.82 ^f (m, 3H, Ar), 8.13-8.34 (m, 2H, Ar), 13.01 (br s, 1H, NH) ^g	294 (M ⁺ , 34), 119 (32), 85 (47), 71 (66), 57 (100)	C ₁₄ H ₆ N ₂ OF ₄	57.16/2.06/9.52 (57.20/2.00/9.50)
6f	278-282 ^d	3170, 1670	7.63-7.81 ^f (m, 3H, Ar), 7.92-8.01 (m, 1H, Ar) 8.13-8.41 (m, 2H, Ar), 12.90 (br s, 1H, NH) ^g	276 (M ⁺ , 100), 173 (72), 144 (13), 104 (10), 77 (25)	C ₁₄ H ₇ N ₂ OF ₃	60.88/2.55/10.14 (60.70/2.40/10.10)
6g	238-242 ^h	3160, 1690	2.42 ^f (s, 3H, Me), 12.69 (br s, 1H, NH) ^g	232 (M ⁺ , 100), 214 (90), 191 (25)	C ₉ H ₄ N ₂ OF ₄	46.57/1.74/12.07 (46.40/1.60/12.00)
6h	292-294 ^d	3180, 1684	2.38 (s, 3H, Me) 7.52-7.60 (m, 1H, Ar) 12.52 (br s, 1H, NH) ^g	214 (M ⁺ , 100), 173 (19), 146 (15)	C ₉ H ₅ N ₂ OF ₃	50.48/2.35/13.08 (50.30/2.30/13.00)

^a Lit.,¹⁵ mp 249-250 °C

^b Lit.,¹⁵ mp 160-161 °C

^c Lit.,¹⁵ mp 181.5-182.5 °C

^d Crystallization solvent: Ethanol

^e in acetone-d₆.

^f in DMSO-d₆.

^g exchangeable with D₂O.

^h Crystallization solvent: Benzene.

EXPERIMENTAL

General: Melting points were determined on a REICHART-THERMOVAR hot-stage apparatus and are uncorrected. IR spectra (Nujol) were determined with a PERKIN ELMER 257 instrument; ¹H-NMR

spectra were recorded on a BRUKER AC 250 E spectrometer, and GC/MS determinations were carried out on a VARIAN STAR 3400 CX/SATURN 2000 system. Fluorescence emission spectra were determined in methanol using a JASCO FP-777WI spectrofluorimeter. Flash chromatography was performed by using silica gel (Merck, 0.040-0.063 mesh) and mixtures of ethyl acetate and light petroleum (fraction boiling in the range 40-60°C) in various ratios. Dry methanol and acetonitrile (from Romil Pure Chemicals) were used as received.

Compounds (**5a-c**)⁶ and (**5d**)¹⁶ were prepared as reported; compounds (**5e-h** and **7**) were prepared similarly to the reported procedure¹⁷ as described below.

Synthesis of 5-polyfluoroaryl-1,2,4-oxadiazoles (5e-h, 7). General procedure.

A mixture of benzamidoxime (for compound **5e,f** and **7**), or acetamidoxime (for compound **5g,h**) (10 mmol), pyridine (0.9 mL, 11 mmol) and the appropriate polyfluorobenzoyl chloride (11 mmol) was refluxed for 8 h in anhydrous toluene (100 mL). After removal of the solvent, the residue was treated with water and then extracted with EtOAc. The organic layers were dried over Na₂SO₄ and evaporated. Chromatography of the residue gave the oxadiazoles (**5e-h** and **7**) (yields 60-80%).

3-Phenyl-5-(2,3,4,5-tetrafluorophenyl)-1,2,4-oxadiazole (5e), had mp 150-151°C (ethanol), ¹H NMR (CDCl₃) δ 7.27-7.57 (m, 3H, Ar); 7.90-7.95 (m, 1H, Ar); 8.15-8.19 (m, 2H, Ar). MS *m/z* 294 (M⁺, 100), 177 (11), 119 (41). Anal. Calcd for C₁₄H₆N₂OF₄: C, 57.16; H, 2.06; N, 9.52. Found: C,57.10; H,2.00; N, 9.40.

3-Phenyl-5-(2,3,4-trifluorophenyl)-1,2,4-oxadiazole (5f), had mp 144-145°C (ethanol), ¹H NMR (CDCl₃) δ 7.14-7.27 (m, 1H, Ar); 7.50-7.56 (m, 3H, Ar); 7.96-8.05 (m, 1H, Ar); 8.15-8.19 (m, 2H, Ar). MS *m/z* 276 (M⁺, 100), 119 (29), 64 (21). Anal. Calcd for C₁₄H₇N₂OF₅: C, 57.16; H, 2.06; N, 9.52. Found: C,57.10; H,2.00; N, 9.40.

3-Methyl-5-(2,3,4,5-tetrafluorophenyl)-1,2,4-oxadiazole (5g), had mp 150-151°C (ethanol), ¹H NMR (CDCl₃) δ 2.50 (s, 3H, Me); 7.72-7.77 (m, 1H, Ar);. MS *m/z* 232(M⁺, 100), 175 (14), 58 (15). Anal. Calcd for C₉H₄N₂OF₄: C, 46.57; H, 1.74; N, 12.07. Found: C, 46.50; H,1.70; N, 12.00.

3-Methyl-5-(2,3,4-trifluorophenyl)-1,2,4-oxadiazole (5h), had mp 72-73°C (light petroleum), ¹H NMR (CDCl₃) δ 2.51 (s, 3H, Me); 7.11-7.22 (m, 1H, Ar); 7.83-7.92 (m, 1H, Ar); MS *m/z* 214(M⁺, 100), 157 (12). Anal. Calcd for C₉H₅N₂OF₃: C, 50.48; H, 2.35; N, 13.08. Found: C, 50.50; H,2.30; N, 12.90.

3-Phenyl-5-pentafluorophenyl-1,2,4-oxadiazole (7), had mp 132°C (ethanol); ¹H-NMR (CDCl₃) δ 7.53-7.71 (m, 3H), 8.21-8.25 (m, 2H); MS *m/z* (312 M⁺ 100), 195 (25), 119 (81), 91 (46), 63 (54). C₁₄H₅N₂OF₅: C, 53.86; H, 1.61; N, 8.97. Found: C, 53.80; H,1.50; N, 8.90.

General Procedure for Photochemical Reactions

Photochemical reactions were carried out by using a Rayonet RPR-100 photoreactor fitted with 16 Hg lamps irradiating at $\lambda = 313$ nm (RPR 3000Å) and $\lambda = 365$ nm (RPR 3650Å) and equipped with a merry-go-round apparatus.

Irradiations at $\lambda = 313$ nm in the presence of TEA.

A solution of compounds (**5a-h**) (1.5 mmol) in anhydrous acetonitrile (150 ml), was partitioned into six pyrex tubes and purged with nitrogen (10 min). An excess of TEA (Molar ratio TEA/oxadiazole = 10/1) was added and all the samples were irradiated for 2 h (4 h for **5a-c**). The solvent was evaporated to dryness under reduced pressure yielding a residue that was chromatographed with light petroleum/ethyl acetate at various ratios. Yields and spectroscopic data are respectively reported in Tables 1 and 3.

Irradiations at $\lambda = 365$ nm in the presence of Pyrene.

A solution of compounds (**5a-h**) (1.5 mmol) in anhydrous methanol (for compounds **5a-c**) or acetonitrile (for compounds **5d-h**) (150 mL) containing pyrene as sensitizer (0.6 g, 3 mmol), was partitioned into six pyrex tubes, purged with nitrogen (10 min) and irradiated for 5 h. Yields and spectroscopic data are respectively reported in Tables 1 and 3

Irradiations of compound **7** at $\lambda = 365$ nm in the presence of pyrene.

Irradiation of the compound (**7**) in acetonitrile in the presence of pyrene gave recovered starting material (50%) and *N*-pentafluorobenzoylbenzamidine (**9**) (20%).

Compound (**9**) had mp 287-290 °C (ethanol), IR 3420, 3320, 3220, 1670 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ 7.55-7.72 (m, 3H), 7.90-8.15 (m, 2H), 9.93 (s, 1H), 10.30 (s, 1H); MS m/z (314 M^+ 30), 195 (62), 167 (66), 147 (100), 117 (23), 104 (65), 77 (68), 63 (54). $\text{C}_{14}\text{H}_7\text{N}_2\text{OF}_5$: C, 53.52; H, 2.25; N, 8.92. Found: C, 53.40; H, 2.10; N, 8.80.

ACKNOWLEDGEMENT

Financial support through the Italian MIUR and University of Palermo within the National Research Projects "Fluorinated Compounds: New Materials for Advanced Applications" (PRIN 2001) and "Fluorinated Nanoreactors with Designed Structures and Optimised Functions" (PRIN 2003) is gratefully acknowledged.

REFERENCES

- 1 (a) K. Burger, U. Wucherpfennig, and E. Brunner, *Adv. Heterocycl. Chem.*, 1994, **60**, 1, and references cited therein; (b) E. Differding, W. Frick, R. W. Lang, P. Martin, C. Schmit, S. Veenstra, and H. Greuter, *Bull. Soc. Chim. Belg.*, 1990, **99**, 647; (c) J. C. Sloop, C. L. Bumgardner, and W. D. Loehle., *J. Fluorine Chem.*, 2002, **118**,135; (d) S. Z. Zhu, Y. L. Wang, W. M. Peng, L. P. Song, and G. F. Jin, *Curr. Org. Chem.*, 2002, **6**, 1057.
- 2 (a) N. Vivona, and S. Buscemi, *Heterocycles*, 1995, **41**, 2095; (b) S. Buscemi, N. Vivona, and T. Caronna, *J. Org. Chem.*, 1995, **60**, 4096; (c) S. Buscemi, N. Vivona, and T. Caronna, *J. Org. Chem.*, 1996, **61**, 8397; (d) N. Vivona, S. Buscemi, S. Asta, and T. Caronna, *Tetrahedron*, 1997, **53**, 12629.
- 3 S. Buscemi, A. Pace, N. Vivona, T. Caronna, and A. Galia, *J. Org. Chem.*, 1999, **64**, 7028.
- 4 S. Buscemi, A. Pace, N. Vivona, and T. Caronna, *J. Heterocycl. Chem.*, 2001, **38**, 777.
- 5 (a) S. Buscemi, A. Pace, and A. Vivona, *Tetrahedron Lett.*, 2000, **41**, 7977; (b) S. Buscemi, A. Pace, R. Calabrese, N. Vivona, and P. Metrangolo, *Tetrahedron*, 2001, **57**, 5865; (c) S. Buscemi, A. Pace, I. Pibiri, and N. Vivona, *Heterocycles*, 2002, **57**, 1891; (d) S. Buscemi, A. Pace, I. Pibiri, N. Vivona, and D. Spinelli, *J. Org. Chem.*, 2003, **68**, 605.
- 6 S. Buscemi, A. Pace, I. Pibiri, N. Vivona, C. Zaira Lanza, and D. Spinelli, *Eur. J. Org. Chem.*, 2004, 974.
- 7 G. Daidone, D. Raffa, B. Maggio, F. Plescia, V. M. C. Cutulli, N. G. Mangano, and A. Caruso, *Arch. Pharm. Pharm. Med. Chem.*, 1999, **332**, 50.
- 8 P. Pramella, E. Rajanernder, and A. K. Murty, *Indian J. Heterocycl. Chem.*, 1992, **2**, 115.
- 9 V. K. Srivastava, S. Singh, A. Gulati, and K. J. Shaker, *Ind. Vhem. Sect. B*, 1987, **26**, 652.
- 10 J. Fetter, T. Czuppon, G. Hornyak, and A. Feller, *Tetrahedron* , 1991, **47**, 9393.
- 11 (a) J. B. Jiang, D. P. Hesson, B. A. Dusak, D. L. Dexter, G. J. Kang, and E. Hamel, *J. Med. Chem.*, 1990, **33**, 1721; (b) M. Kuo, M. Hour, L. Huang, and K. Lee, US Patent 2002 (*Chem. Abstr.*, 2002, **137**, 353059); (c) K. E. Lackey, N. Spector, E. R. Wood, and W. Xia, Patent 2002 (*Chem. Abstr.*, 2002, **137**, 555376).
- 12 M. Shyimad, R. Kalsi, K. S. Dixit, and J. P. Bartwal, *Arzneim.-Forsch/Drug Res.*, 1991, **41**, 514.
- 13 S. Archana and A. Kumar, *Eur. J. Med. Chem.*, 2002, **37**, 873.
- 14 P. A. Carpini, US Patent 2002 (*Chem. Abstr.*, 2002, **136**, 85820).
- 15 J. Greiner, R. Pastor, and A. Cambon, *J. Fluorine Chem.*, 1981, **18**, 185.
- 16 G. S. Shchegoleva, V. A. Barkhash, and N. N. Vorozhtsov Jr., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1967, **3**, 708 (*Chem. Abstr.*, 1967, **67**, 100075).

- 17 (a) S. Borg, G. Estenne-Bouhtou, K. Luthman, I. Csoregh, W. Hesselink, and U. Hacksell, *J. Org. Chem.*, 1995, **60**, 3112. (b) J. Saunders, M. Cassidy, S. B. Freedman, E. A. Harley, L. L. Iversen, C. Kneen, A. M. Macleod, K. J. Merchant, R. J. Snow, and R. Baker, *J. Med. Chem.*, 1990, **33**, 1128. (c) B. S. Orlek, F. E. Blaney, F. Brown, M. S. G. Clark, M. S. Hadley, J. Hatcher, G. J. Riley, H. E. Rosenberg, H. J. Wadsworth, and P. Wyman, *J. Med. Chem.*, 1991, **34**, 2726. (d) G. D. Diana, D. L. Volkots, T. J. Nitz, T. R. Bailey, M. A. Long, N. Vescio, S. Aldous, D. C. Pevear, and F. J. Dutko, *J. Med. Chem.*, 1994, **37**, 2421. (e) W. S. Messer Jr., Y. F. Abuh, Y. Liu, S. Periyasamy, D. O. Ngur, M. A. N. Edgar, A. A. Zl-Assadi, S. Sbeih, P. G. Dunbar, S. Roknich, T. Rho, Z. Fang, B. Ojo, H. Zhang, J. J. Huzl III, and P. I. Nagy, *J. Med. Chem.*, 1997, **40**, 1230.
- 18 (a) K. Hirakawa and H. Segawa, *J. Photochemistry and Photobiology A: Chemistry*, 1999, **123**, 67; (b) S. Hashimoto, *Chem. Phys. Lett.*, 1996, **252**, 236.