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Fluoro heterocycles. A photochemical methodology for the synthesis of 3-amino- and 3-(*N*-alkylamino)-5-perfluoroalkyl-1,2,4-oxadiazoles

Silvestre Buscemi, Andrea Pace and Nicolò Vivona*

Dipartimento di Chimica Organica 'E. Paternò', Università degli Studi di Palermo, Viale delle Scienze-Parco D'Orleans II, 90128 Palermo, Italy

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Abstract

A photochemical methodology for the synthesis of perfluoroalkyl-1,2,4-oxadiazoles has been described. 3-Amino- and 3-(*N*-alkylamino)-5-perfluoroalkyl-1,2,4-oxadiazoles have been prepared by irradiation of 3-perfluoroalkanoylamino-4-phenyl-1,2,5-oxadiazoles (furazans) at $\lambda = 313$ nm in methanol and in the presence of ammonia or primary aliphatic amines.

Keywords: perfluoroalkanoylamino-furazans; photolysis; perfluoroalkylheterocycles; oxadiazoles.

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 fluorinating or perfluoroalkylating reagents, a widely used approach to fluorinated heterocycles uses building-block strategies, e.g. by the formation of the heterocyclic ring from fluorinated precursors.[1] In this context, a very promising strategy can be recognized in photochemical methodologies exploiting photoinduced rearrangements of suitable heterocyclic structures, such as O–N bonds containing azoles.[2] As part of a research program on the synthesis and reactivity of fluorinated derivatives of five-membered heterocycles, we became interested in realizing an efficient and general synthesis of 3-amino- and 3-(*N*-alkylamino)-5-perfluoroalkyl-1,2,4-oxadiazoles. To this purpose, it is worthy to note that in the last few years increasing efforts have been devoted to develop synthetic methods for targeting 1,2,4-oxadiazoles,[3] and this is because 1,2,4-oxadiazole moieties have some interest in the pharmaceutical industry.[4] So, for 3-amino- or 3-(*N*-alkylamino)-5-alkyl-1,2,4-oxadiazoles, a new and quite general synthetic approach exploits photochemical methodologies.[2a,5] Thus, irradiation (at

* Corresponding author. Fax: +39 091 596825; e-mail: nvivona@unipa.it

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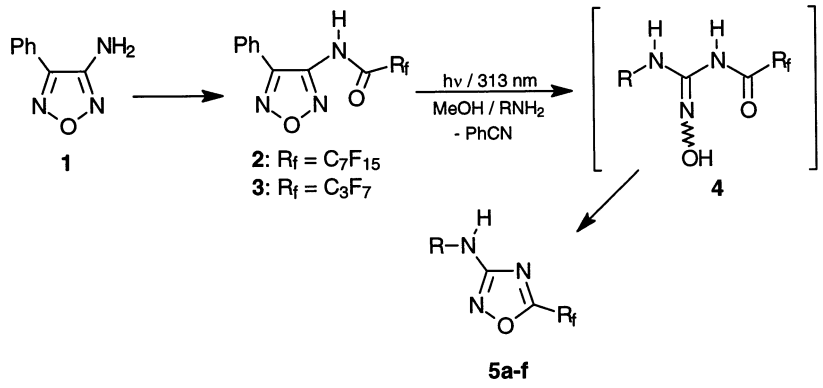
$\lambda = 313$ nm) of 3-alkanoylamino-4-phenyl-1,2,5-oxadiazoles (furazans) in methanol containing ammonia, or primary aliphatic amines gave the mentioned compounds as a result of: (i) photoinduced regioselective-breaking of the 1,2,5-oxadiazole ring involving extrusion of benzonitrile; (ii) capture of the ring-cleaved intermediate by the added amine forming *N*-acylaminoamidoximes which will undergo cyclo-dehydration into final products in the reaction medium.[5]

On this basis, to realize our aim we decided to pursue this photochemical approach by studying the photochemistry of 3-perfluoroalkanoylamino-4-phenylfurazans, with the assumption that the perfluoroalkyl moiety would preserve the regioselective-breaking of the O(1)–N(2) bond of the furazan nucleus on one hand, and would favour the heterocyclization step, on the other. In this communication we report preliminary results[6] concerning irradiation of perfluoroalkanoylamino-furazans **2** and **3** at $\lambda = 313$ nm in the presence of ammonia or some primary aliphatic amines (see Scheme 1).



Scheme 1.

Compounds **2** and **3** have been prepared (in 80% yield) by a standard protocol,[5] that is, by the acylation reaction of the 3-aminofurazan (**1**)[7] with the appropriate perfluoroacyl chloride (for **2**) or perfluoroanhydride (for **3**).[8,9] As for photochemical experiments,[10] we observed that the photochemistry of these substrates was significantly dependent on the concentration of the amine and irradiation time. At variance with 3-amino- or 3-(*N*-alkylamino)-5-alkyl-1,2,4-oxadiazoles, the expected 5-perfluoroalkyl derivatives showed some photoreactivity under the reaction conditions.

Therefore, irradiations had to be carried out at low conversion of starting material. Thus, a typical irradiation of **2** (1 mmol) in methanol (200 mL) in the presence of, respectively, ammonia, methylamine, *n*-propylamine, and *n*-octylamine (2.5 mmol) at $\lambda = 313$ nm for 60 min gave the 3-amino- (**5a**) and 3-(*N*-alkylamino)-5-perfluoroalkyl-oxadiazoles (**5b–d**), respectively. Similarly, irradiation of **3** for 90 min in the presence of methanolic ammonia or methylamine gave oxadiazoles **5e** and **5f**, respectively (see Table 1). To compare, a sample of **5a** was also obtained, although in very low yields, by acylation and subsequent cyclodehydration of *N*-hydroxyguanidine,[11] exploiting conventional procedures.[12]

As mentioned above, the whole reaction goes through a thermal cyclo-dehydration of *N*-acylamino-amidoxime intermediates **4**. Following photolysis of **2** in the presence of methylamine by HPLC, we found that when the irradiation was stopped, the concentration of final oxadiazole **5b** was low. By standing the photolysate in the dark for 24 h, the concentration of

Table 1
Irradiation of 3-alkanoylamino-4-phenylfurazans (**2**, **3**): preparation of 3-amino- and 3-(*N*-alkylamino)-5-perfluoroalkyl-1,2,4-oxadiazoles **5a**–**f**[8]

Substrate	RNH_2 (R)	Product	Yield (%)	Mp[a] (°C)	^1H NMR (DMSO-d_6/TMS) δ, J (Hz)	MS m/z
2	H	**5a**	40	103	7.15 (s)[b]	453 (M^+), 134, 69, 58
2	CH_3	**5b**	50	59	2.80 (d, 3H, $J=5$)[c], 7.60 (q, 1H, $J=5$)[b]	467 (M^+), 119, 72, 69, 42
2	n-C_3H_7	**5c**	45	38	0.99 (t, 3H, $J=7$), 1.64–1.74 (m, 2H), 3.27 (q, 2H, $J=7$), 4.62 (broad, 1H)[d]	495 (M^+), 466, 169, 126, 69, 43
2	n-C_8H_{17}	**5d**	40	54	0.89 (t, 3H, $J=7$), 1.29–1.40 (m, 10H), 1.59–1.71 (m, 2H), 3.26–3.34 (m, 2H), 4.57 (t, 1H, $J=6$)[b,d]	565 (M^+), 466, 196, 69, 43
3	H	**5e**	30	71	7.14 (s)[b]	253 (M^+), 234, 196, 169, 134, 119, 69, 58
3	CH_3	**5f**	30	49	2.82 (d, 3H, $J=5$)[c], 7.63 (broad, 1H)[b]	267 (M^+), 239, 196, 169, 119, 69, 42

[a] Crystallization solvent: light petroleum (fraction boiling between 40 and 60°C).
[b] Exchangeable with D_2O.
[c] Singlet in the presence of D_2O.
[d] In $CDCl_3$.

5b increases as a result of thermal evolution of the supposed *N*-acylamidoxime **4**. On this basis, experimental conditions allowed us to isolate oxadiazoles **5a**–**f** with yields in the range of 30–50% (30–40% of starting material being recovered) by simply standing the photolysate for 24 h before the usual work-up procedure. Nevertheless, these yields could be further optimized by varying irradiation or standing conditions.

Although at first glance yields do not appear excellent, if compared with troublesome non-photochemical procedures, this photochemical approach can be considered a general and efficient method for the synthesis of 3-amino-, and, particularly, of 3-(*N*-alkylamino)-5-perfluoroalkyl-1,2,4-oxadiazoles (with a chosen length of the chain both at the *N*-alkyl moiety and at the perfluoroalkyl group); moreover, it opens new and promising strategies in the synthesis of perfluoroalkyl-heterocycles. A complete study on the photoreactivity of 3-perfluoroalkanoylamino-furazans irradiated in the presence of aliphatic amines, as well as on the photoreactivity of 5-perfluoroalkyl-1,2,4-oxadiazoles formed will follow.

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8. Satisfactory elemental analyses were obtained for all new compounds.
9. Compound **2** had mp 93°C (from benzene/light petroleum); IR (nujol mull): 3270, 1725 cm^{-1}; UV–vis: $\lambda_{max}=240$ nm ($\log \varepsilon=4.0$); ^1H NMR (DMSO-d_6) δ: 7.42–7.78 (m, 5H), 12.8 (br s, 1H); Mass e/z: 557 (M^+), 527, 119, 104, 69. Compound **3** had mp 97°C (from benzene/light petroleum); IR (nujol mull): 3260, 1725 cm^{-1}; UV–vis: $\lambda_{max}=251$ nm ($\log \varepsilon=3.7$); ^1H NMR (DMSO-d_6) δ: 7.59–7.79 (m, 5H), 12.9 (br s, 1H); mass e/z: 357 (M^+), 327, 169, 119, 104, 77, 69.

10. Photochemical reactions were carried out in anhydrous methanol (in 25 mL Pyrex vessels) by using a Rayonet RPR-100 photoreactor equipped with 16 Hg lamps irradiating at $\lambda = 313$ nm (RPR-3000 Å lamps) and a merry-go-round apparatus.
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