A Generalized and Efficient Synthesis of 3-Amino-, 3-(*N*-Alkylamino)-, 3-(*N*,*N*-Dialkylamino)-5-alkyl-1,2,4-oxadiazoles by Irradiation of 3-Alkanoylamino-4-phenyl-1,2,5-oxadiazoles (Furazans)

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Irradiation of 3-alkanoylamino-4-phenyl-1,2,5-oxadiazoles (furazans) at $\lambda = 310$ nm in methanol and in the presence of ammonia, primary or secondary aliphatic amines produced excellent yields of 3-amino-, 3-(*N*-alkylamino)-, 3-(*N*,*N*-dialkylamino)-5-alkyl-1,2,4-oxadiazoles.

In the course of our work on molecular rearrangements of five-membered heterocycles,[1] we became interested in a generalized and efficient synthesis of 5-alkyl-3-amino-1,2,4-oxadiazoles and their *N*-alkyl or *N*,*N*-dialkyl derivatives. This appeared to be of some interest since there are difficulties in their preparation by conventional methods.[2] It is known that synthesis of 3-aminooxadiazoles (but not their *N*-substituted derivatives) are obtained by the reaction of *N*-acylcyanamides,[3,4] or *N*-cyanoamidines[5] with hydroxylamine. Other methods (which have been also used for the synthesis of *N*-substituted compounds) of preparation are the reaction of *N*-benzoyl-*S*-methylisothioureas[6] with hydroxylamine and oxidative cyclization of *N*-acylguanidines.[7] In some instances,[8,9] 3-(*N*-substituted amino)-5-phenyl-1,2,4-oxadiazoles have been obtained from 3-chloro or 3-bromo compounds by nucleophilic displacement of the halide ion with primary or secondary aliphatic amines. On the other hand, this latter reaction does not appear to be widely used for the synthesis of 3-amino-, or 3-(*N*-substituted amino)-5-alkyl derivatives; 3-halo-5-alkyloxadiazoles are not always easily accessible.[10]

In connection with a photochemical study,[9,11] we reported that irradiation of some 3-aroylamino-1,2,5-oxadiazoles (furazans) at $\lambda = 254$ nm in methanol and in the presence of ammonia, primary or secondary aliphatic amines produced 3-substituted 1,2,4-oxadiazoles in which the substituent at C(3) arises from the reagent which was used. This photoreaction, which has been explained as proceeding through an initial photoinduced ring fragmentation involving the O(1)–N(5) bond of the furazan ring, followed by a ring closure of an aroylamino–amidoxime intermediate, has been claimed as a possible methodology for the synthesis of 3-amino-, or 3-(*N*-substituted amino)-1,2,4-oxadiazoles. A restriction has been recognised on the availability of the appropriate amine, and, more significantly, on the subsequent photoreactivity of resulting oxadiazoles which limits the potential synthetic utility of the reaction.

In the same context, we also observed[11] that in the irradiation of 3-acetylamino-4-phenylfurazan at 254 nm in methanolic amines (pyrrolidine, methylamine), the expected ring fragmentation engaged both O–N bonds of the ring. For its part, the pathway involving cleavage of the O(1)–N(5) bond leads to the expected 3-substituted 5-methyl-1,2,4-oxadiazoles.

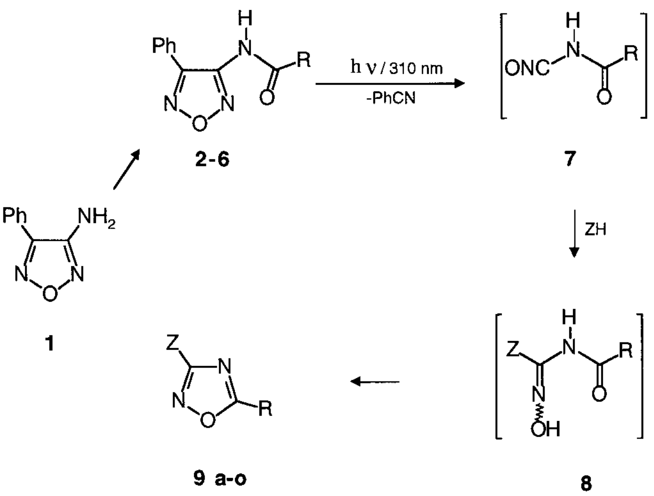
To reach our purposes, we therefore exploited photoinduced rearrangements of suitable 3-alkanoylamino-4-phenylfurazans (representatively, compounds **2–6**), which were easily obtained from the 3-amino-4-phenylfurazan (**1**) and alkanoyl chlorides (Table 1). At variance with irradiation conditions which were previously used,[9,11] here we considered irradiations at $\lambda = 310$ nm (using 16 lamps in a Rayonet apparatus) by using Pyrex vessels. The choice of these conditions was of some significance. First of all, the resulting 3-substituted 5-alkyl-1,2,4-oxadiazoles were weakly photoreactive at $\lambda = 310$ nm, thus minimizing subsequent photoreactions. Moreover, and interestingly, irradiation at $\lambda = 310$ nm in the presence of amines essentially resulted in a selective fragmentation at the O(1)–N(5) bond of the furazan ring. Thus irradiation of compounds **2–6** in methanolic ammonia, primary or secondary aliphatic amines (representatively: methylamine, dimethylamine, butylamine, pyrrolidine), gave benzonitrile and the corresponding 3-amino- (or substituted amino) oxadiazoles **9a–o** which can be easily isolated in excellent yields (Table 2). It is noteworthy that these photoreactions proceed with complete conversion of the starting material, thus suggesting that this route can be really considered

Table 1. 3-Alkanylamino-4-phenylfurazans **2–6** Prepared

Product	R	mp (°C)	IR (Nujol) ν (cm^{-1})	^{1}H NMR (DMSO-d_6/TMS) δ, J (Hz)
2	Me	183[a]		
3	Et	132	3250, 3220, 1700	1.21 (t, 3H, $J = 8$), 2.52 (q, 2H, $J = 8$), 7.64–7.82 (m, 5H), 10.78 (s, 1H)
4	Pr	111	3260, 3220, 1695	0.95 (t, 3H, $J = 7$), 1.56–1.67 (m, 2H), 2.44 (t, 2H, $J = 7$), 7.58–7.80 (m, 5H), 10.77 (s, 1H)
5	Bu	94	3250, 1690	0.94 (t, 3H, $J = 7$), 1.27–1.42 (m, 2H), 1.53–1.65 (m, 2H), 2.46 (t, 2H, $J = 7$), 7.59–7.80 (m, 5H), 10.76 (s, 1H)
6	PhCH$_2$	155	3220, 1670	3.78 (s, 2H), 7.30–7.60 (m, 10H), 11.04 (s, 1H)

[a] Lit.[14] mp 181–182 °C

a generalized and efficient methodology for the synthesis of our target oxadiazoles.



As for mechanistic aspects, the reaction could be roughly explained by assuming the expected nitrile oxides **7** and then *N*-acylamidoximes **8** as intermediates. A more intriguing pathway could be an initially formed complex between acylamino compounds and the amine as the actual photoreactive species from which the selective fragmentation at the O(1)–N(5) bond of the furazan ring would take place. A support to this hypothesis could be recognized in the lower photoreactivity of our substrates when irradiated in the absence of an amine. A deeper mechanistic investigation will be however discussed in a separate work.

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer 257 instrument, ^{1}H NMR spectra were recorded on a Bruker 250 E spectrometer and mass spectra (70 eV) with a RMU-60 instrument. Flash chromatography[12] was performed on Merck silica gel by using mixtures of light petroleum (fraction boiling in the range of 40–60 °C) and EtOAc in varying ratios. Freshly prepared saturated methanolic ammonia, ethanolic (33 %) methylamine and dimethylamine (Fluka), and freshly distilled butylamine or pyrrolidine (Aldrich) were used. 3-Alkanoylamino-4-phenylfurazans **2–6** were prepared by reacting 3-amino-4-phenylfurazan[13] **(1)** (1.6 g, 10 mmol) with the appropriate alkanoyl chloride (12 mmol) in anhydr. benzene (100 mL) containing pyridine (1.0 mL, 12 mmol) at reflux (3 h). After removal of the solvent, the residue was worked up with H_2O and filtered to give crude alkanoylamino compounds which were purified by crystallization from benzene or, in some instances, by chromatography; Yields: 70–80 % (Table 1). Analytical samples were crystallized from benzene. Photochemical reactions were carried out in anhydr. MeOH in Pyrex vessels, by using a Rayonet RPR-100 photoreactor, fitted with 16 irradiating lamps at $\lambda = 310$ nm and a merry-go-round apparatus. Satisfactory microanalyses were obtained for all new compounds: C ± 0.15, H ± 0.14, N ± 0.16.

Irradiation of 3-Alkanoylamino-4-phenylfurazans 2–6; General Procedure:

To a sample of the alkanoylamino compound **2–6** (0.5 g) in MeOH (90 mL) was added a large excess of the appropriate amine [namely: methanolic ammonia (20 mL), ethanolic methylamine or dimethylamine (5 mL), butylamine (2 mL) or pyrrolidine (2 mL)]. The solution was apportioned into six Pyrex tubes and then irradiated for 90 minutes. After removal of the solvent, the residue was chroma-

Table 2. Irradiation of Alkanoylaminofurazans **2–6**: Preparation of Compounds **9a–o**

Substrate	ZH[a]	Product	R	Z	Yield[b] (%)	mp (°C)	^{1}H NMR (DMSO-d_6/TMS) δ, J (Hz)	MS m/z
2	A	**9a**	Me	NH_2	80	117[c,d]	–	
2	B	**9b**	Me	MeNH	95	75[e,f]	–	
2	C	**9c**	Me	$(Me)_2N$	70	oil	2.43 (s, 3 H), 2.98 (s, 6 H)[g]	127 (M^+), 86, 56
2	D	**9d**	Me	BuNH	95	62[f]	0.93 (t, 3 H, $J = 7$), 1.31–1.40 (m, 2 H), 1.51–1.57 m, 2 H), 2.42 (s, 3 H), 3.04–3.12 (m, 2 H), 6.72 (t, 1 H, $J = 5$)	155 (M^+), 140, 118, 70
2	E	**9e**	Me	$(CH_2)_4N$	90	oil[h]	–	
3	A	**9f**	Et	NH_2	80	47[f]	1.22 (t, 3 H, $J = 8$), 2.72 (q, 2 H, $J = 8$), 6.13 (s, 2 H)	113 (M^+), 56
3	B	**9g**	Et	MeNH	85	43[f]	1.22 (t, 3 H, $J = 8$), 2.67–2.76 (m, 5 H),[i] 6.58 (br q, 1 H)	127 (M^+), 99, 72
3	C	**9h**	Et	$(Me)_2N$	70	oil	1.34 (t, 3 H, $J = 8$), 2.77 (q, 2 H, $J = 8$), 3.00 (s, 6 H)[g]	141 (M^+), 86, 56
4	A	**9i**	Pr	NH_2	90	101[f]	0.93 (t, 3 H, $J = 7$), 1.64–1.73 (m, 2 H), 2.68 (t, 2 H, $J = 7$), 6.14 (s, 2 H)	127 (M^+), 99, 70
4	B	**9j**	Pr	MeNH	80	oil	0.97 (t, 3 H, $J = 8$), 1.66–1.81 (m, 2 H), 2.71–2.77 (m, 5 H),[i] 6.67 (q, 1 H, $J = 5$)	141 (M^+), 113, 72
5	A	**9k**	Bu	NH_2	85	62[f]	0.90 (t, 3 H, $J = 8$), 1.27–1.41 (m, 2 H), 1.59–1.71 (m, 2 H), 2.70 (t, 2 H, $J = 8$), 6.11 (s, 2 H)	141 (M^+), 112, 99, 84
5	B	**9l**	Bu	MeNH	95	33[f]	0.95 (t, 3 H, $J = 7$), 1.32–1.46 (m, 2 H), 1.64–1.76 (m, 2 H), 2.73–2.80 (m, 5 H),[i] 6.68 (q, 1 H, $J = 5$)	155 (M^+), 126, 113, 72
6	A	**9m**	$PhCH_2$	NH_2	80	117[d,j]	–	
6	B	**9n**	$PhCH_2$	MeNH	90	92[f]	2.68 (d, 3 H, $J = 5$),[k] 4.11 (s, 2 H), 6.64 (q, 1 H, $J = 5$), 7.28–7.35 (m, 5 H)	189 (M^+), 91, 72
6	E	**9o**	$PhCH_2$	$(CH_2)_4N$	90	49[f]	1.96–2.01 (m, 4 H), 3.42–3.47 (m, 4 H), 4.12 (s, 2 H), 7.29–7.37 (m, 5 H)[g]	229 (M^+), 91, 70

[a] A = NH_3, B = $MeNH_2$, C = $(Me)_2NH$, D = $BuNH_2$, E = pyrrolidine.

[b] Yield of isolated product.

[c] Lit.[15] mp 117–119 °C.

[d] Crystallization solvent: benzene.

[e] Lit.[11] mp 75–76 °C.

[f] Crystallization solvent: light petroleum.

[g] Solvent: $CDCl_3$.

[h] Lit.[11] oil.

[i] Includes a doublet ($J = 5$ Hz, $NHC\underline{H}_3$).

[j] Lit.[3] mp 115–117 °C.

[k] Singlet in the presence of D_2O.

tographed to give benzonitrile and then oxadiazoles **9a–o**, which were purified by crystallization or by subsequent chromatography (Table 2).

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