SYNTHESIS OF 2,5-DISUBSTITUTED 1,3,4-OXADIAZOLES AND THEIR PRECURSORS

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The characteristic feature of many commercial agrochemicals and drugs is the 5-nitro-2-furyl or 2,5-dimethyl-3-furyl building block[1,2]. Within the scope of our research aimed at utilization of dipolar cycloaddition reactions to prepare new compounds with potential biological and phytoeffectorial activity, we report on the synthesis of some substituted hydrazones *I* and their intramolecular cycloaddition to 2,5-disubstituted 1,3,4-oxadiazoles *II*. The basic IR, ^{1}H NMR as well as mass spectral data of final products are presented.

EXPERIMENTAL

The melting points are uncorrected, the IR spectra (ν, cm^{-1}) were taken with Philips analytical PU 9800 FTIR spectrometer in KBr pellets, the ^{1}H NMR spectra (δ, ppm; *J*, Hz) of hexadeuteriodimethyl sulfoxide solutions containing tetramethylsilane as an internal standard were recorded on Tesla BS 487 C spectrometer (80 MHz). Mass spectra (*m*/*z*, rel.%) were recorded on AEI spectrometer MS 902 S with direct inlet and ionizing energy of 70 eV, capture current 100 μA and the temperature of ionizing chamber 80 – 215 °C. Starting substituted 5-aryl-2-furancarbaldehydes were prepared according to refs[3–5], the requisite 2-furoyl- and 2,5-dimethyl-3-furoylhydrazides according to ref.[6].

Substituted Hydrazones *I*. General Procedure

The mixture of respective aldehyde (0.01 mol) and corresponding hydrazide of furancarboxylic acid (0.01 mol) dissolved in ethanol (50 – 80 ml) was refluxed for 1 – 4 h (monitoring by TLC, ref.[7]). After cooling to room temperature the separated solid was crystallized from ethanol or dioxane to afford pure product. The characteristic data of prepared hydrazones are summarized in Table I.

2,5-Disubstituted Oxadiazoles *II*. General Procedure

Method A: To stirred suspension of hydrazone *I* (3 mmol) in dichloromethane (100 ml) was added lead tetraacetate (1.77 g, 3 mmol) at room temperature and the reaction mixture was kept under reflux for several hours (monitoring by TLC). After the undissolved materials were filtered off, the solvent was removed under reduced pressure. The residue was recrystallized from suitable solvent, or purified on silica gel (chloroform).

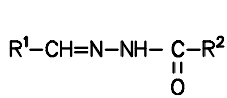
Method B: A mixture of respective hydrazone *I* (7 mmol) and NiO_2 (2.6 g) in chloroform (175 ml) was refluxed for 6 h. After inorganic materials were filtered off, the solvent was removed under reduced pressure and the crude product was purified in the manner described in Method *A*.

2-Phenyl-5-(2-furyl)-1,3,4-oxadiazole (*IIa*)

Yield 47% (method *A*), m.p. 96 – 98 °C. For $C_{12}H_8N_2O_2$ (212.2) calculated: 67.91% C, 3.80% H, 13.20% N; found: 67.58% C, 3.61% H, 13.07% N. ^{1}H NMR spectrum: 6.22 dd, 1 H, J = 1.8 (H-4); 7.23 d, 1 H, J = 3.5 (H-3); 7.57 – 7.48 m, 3 H (H arom.). Mass spectrum: 212 (M^+, 100), 156 (16), 128 (46), 105 (67), 102 (31), 95 (46), 77 (48), 51 (16). IR spectrum: 1 632 (C=N).

2-(5-Nitro-2-furyl)-5-(2-furyl)-1,3,4-oxadiazole (*IIb*)

Yield 82% (method *A*), 86% (method *B*), m.p. 258 – 260 °C. For $C_{10}H_5N_3O_5$ (247.1) calculated: 48.60% C, 2.04% H, 17.00% N; found: 48.94% C, 2.40% H, 17.14% N. ^{1}H NMR spectrum: 6.81 dd,



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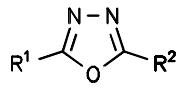

II

I, *II*	R^1	R^2
a	phenyl	2-furyl
b	5-nitro-2-furyl	2-furyl
c	5-(4-nitrophenyl)-2-furyl	2-furyl
d	5-(4-chlorophenyl)-2-furyl	2-furyl
e	5-(4-bromophenyl)-2-furyl	2-furyl
f	5-(4-methoxyphenyl)-2-furyl	2-furyl
g	5-(2-nitrophenyl)-2-furyl	2-furyl
h	4-nitrophenyl	2-furyl
i	4-nitrophenyl	2,5-dimethyl-3-furyl
j	*p*-tolyl	2,5-dimethyl-3-furyl
k	4-chlorophenyl	2,5-dimethyl-3-furyl
l	2-furyl	2,5-dimethyl-3-furyl
m	5-(4-bromophenyl)-2-furyl	2,5-dimethyl-3-furyl
n	5-(4-chlorophenyl)-2-furyl	2,5-dimethyl-3-furyl
o	5-(2-nitrophenyl)-2-furyl	2,5-dimethyl-3-furyl
p	*p*-tolyl	2-furyl
r	4-chlorophenyl	2-furyl

TABLE I
Characteristic data of prepared compounds *I*

Compound	Formula (M.w.)	M.p., °C Yield, %	Calculated/Found			ν(C=O), cm^{-1}
			% C	% H	% N	
Ia	$C_{12}H_{10}N_2O_2$	232 – 234	67.28	4.70	13.08	1 671
	(214.2)	70	67.51	4.52	13.25	
Ib	$C_{10}H_7N_3O_5$	233 – 235	48.19	2.83	16.86	1 665
	(249.2)	95	47.91	3.02	16.55	
Ic	$C_{16}H_{11}N_3O_5$	252 – 254	59.07	3.40	12.91	1 664
	(325.3)	80	59.28	3.24	12.95	
Id	$C_{16}H_{11}ClN_2O_3$	201 – 203	61.06	3.52	8.90	1 658
	(314.7)	70	61.20	3.82	8.77	
Ie	$C_{16}H_{11}BrN_2O_3$	135 – 137	53.51	3.08	7.80	1 656
	(359.1)	70	53.30	3.42	7.63	
If	$C_{17}H_{14}N_2O_4$	227 – 229	65.79	4.54	9.02	1 670
	(310.3)	58	65.54	4.75	9.18	
Ig	$C_{16}H_{11}N_3O_5$	91 – 93	59.07	3.40	12.91	1 672
	(325.3)	82	59.38	3.62	12.94	
Ih	$C_{12}H_9N_3O_4$	268 – 269	55.60	3.50	16.21	1 655
	(259.2)	86	55.78	3.21	16.40	
Ii	$C_{14}H_{13}N_3O_4$	201 – 207	56.19	4.56	14.63	1 670
	(287.2)	68	56.41	4.22	14.50	
Ij	$C_{15}H_{16}N_2O_2$	241 – 243	70.28	6.29	10.93	1 668
	(256.3)	62	70.52	6.47	11.08	
Ik	$C_{15}H_{13}ClN_2O_2$	207 – 209	60.76	4.70	10.12	1 656
	(276.7)	63	60.18	4.67	9.81	
Il	$C_{12}H_{12}N_2O_3$	234 – 236	62.06	5.21	12.06	1 664
	(232.2)	65	62.34	5.47	12.16	
Im	$C_{18}H_{15}BrN_2O_3$	204 – 206	55.83	3.90	7.23	1 658
	(387.2)	55	55.97	3.99	7.16	
In	$C_{18}H_{15}ClN_2O_3$	178 – 180	63.06	4.41	8.17	1 660
	(342.8)	61	63.35	4.63	8.29	
Io	$C_{18}H_{15}N_3O_5$	214 – 215	61.88	4.27	11.89	1 663
	(353.3)	80	61.92	4.49	11.63	
Ip	$C_{13}H_{12}N_2O_2$	168 – 169	68.40	5.30	12.27	1 660
	(228.2)	89	68.14	5.45	12.41	
Ir	$C_{12}H_9ClN_2O_2$	197 – 199	57.91	3.64	11.26	1 668
	(248.8)	87	58.10	3.92	11.35	

1 H, *J* = 1.6 (H-4); 7.44 d, 1 H, *J* = 3.4 (H-3); 7.67 d, 1 H, *J* = 4.0 (H-3′); 7.86 d, 1 H (H-4′); 8.05 d, 1 H (H-5). IR spectrum: 1 632 (C=N), 1 545 $(NO_2)_{as}$, 1 358 $(NO_2)_s$.

2-[5-(4-Chlorophenyl)-2-furyl]-5-(2-furyl)-1,3,4-oxadiazole (*IId*)

Yield 65% (method *A*), 74% (method *B*), m.p. 208 °C. For $C_{16}H_9ClN_2O_3$ (312.7) calculated: 61.45% C, 2.90% H, 8.96% N; found: 61.13% C, 3.06% H, 9.10% N. ^{1}H NMR spectrum: 6.84 dd, 1 H, *J* = 1.8 (H-4); 7.35 d, 1 H, *J* = 3.6 (H-3); 7.45 d, 1 H (H-4′); 7.54 d, 1 H (H-3′); 7.61 d, 2 H, *J* = 8.3 (H arom.); 7.90 d, 2 H (H arom.); 8.10 d, 1 H, *J* = 3.0 (H-5). Mass spectrum: 312 (M^+, 100), 207 (14), 205 (44), 202 (11), 149 (28), 95 (39), 53 (23), 39 (11). IR spectrum: 1 626 (C=N).

2-[5-(4-Bromophenyl)-2-furyl]-5-(2-furyl)-1,3,4-oxadiazole (*IIe*)

Yield 45% (method *A*), 67% (method *B*), m.p. 188 – 190 °C. For $C_{16}H_9BrN_2O_3$ (357.1) calculated: 53.80% C, 2.54% H, 7.84% N; found: 53.41% C, 2.83% H, 7.41% N. ^{1}H NMR spectrum: 6.81 dd, 1 H, *J* = 2.1 (H-4); 7.27 d, 1 H, *J* = 3.6 (H-3′); 7.37 d, 1 H (H-3); 7.45 d, 1 H (H-4′); 7.75 d, 2 H, *J* = 8.3 (H arom.); 7.81 d, 2 H (H arom.); 7.96 d, 1 H, *J* = 2.9 (H-5). Mass spectrum: 357 (M^+, 100), 249 (50), 195 (33), 165 (27), 104 (30), 95 (60), 53 (43). IR spectrum: 1 626 (C=N).

2-[5-(2-Nitrophenyl)-2-furyl]-5–(2-furyl)-1,3,4-oxadiazole (*IIg*)

Yield 76% (method *A*), m.p. 145 – 147 °C. For $C_{16}H_9N_3O_5$ (323.2) calculated: 59.44% C, 2.80% H, 12.99% N; found: 59.12% C, 2.45% N.^{1}H NMR spectrum: 6.78 dd, 1 H, *J* = 2.1 (H-4); 7.07 d, 1 H, *J* = 3.7 (H-3′); 7.34 d, 1 H, *J* = 3.52 (H-3); 7.47 d, 1 H, *J* = 3.5 (H-4′); 7.83 d, 1 H, *J* = 3.9 (H-5); 8.05 – 7.7 m, 4 H (H arom.). IR spectrum: 1 612 (C=N), 1 535 $(NO_2)_{as}$, 1 361 $(NO_2)_s$.

2-(4-Nitrophenyl)-5-(2-furyl)-1,3,4-oxadiazole (*IIh*)

Yield 60% (method *A*), m.p. 228 – 230 °C. For $C_{12}H_7N_3O_4$ (257.2) calculated: 56.03% C, 2.74% H, 16.33% N; found: 56.43% C, 3.10% H, 16.48% N. ^{1}H NMR spectrum: 6.79 dd, 1 H, *J* = 2.0 (H-4); 7.42 d, 1 H, *J* = 3.5 (H-3); 8.02 d, 1 H, *J* = 3.2 (H-5); 8.29 d, 2 H, *J* = 9.04 (H arom.); 8.44 d, 2 H (H arom.). Mass spectrum: 257 (M^+, 100), 150 (26), 95 (92). IR spectrum: 1 642 (C=N), 1 555 $(NO_2)_{as}$, 1 356 $(NO_2)_s$.

2-(4-Chlorophenyl)-5-(2,5-dimethyl-3-furyl)-1,3,4-oxadiazole (*IIk*)

Yield 52% (method *A*), m.p. 177 – 182 °C. For $C_{14}H_{11}ClN_2O_2$ (247.7) calculated: 61.20% C, 4.03% H, 10.20% N; found: 61.42% C, 3.86% H, 10.05% N. ^{1}H NMR spectrum: 1.64 s, 6 H ($2 \times CH_3$); 6.40 s, 1 H (H-4); 7.45 d, 2 H, *J* = 8.3 (H arom.); 7.88 d, 2 H (H arom.). IR spectrum: 1 630 (C=N).

2-(4-Tolyl)-5-(2-furyl)-1,3,4-oxadiazole (*IIp*)

Yield 68% (method *A*), m.p. 135 – 136 °C. For $C_{13}H_{10}N_2O_2$ (226.2) calculated: 69.01% C, 4.45% H, 12.38% N; found: 68.93% C, 4.09% H, 12.20% N. ^{1}H NMR spectrum: 2.44 s, 3 H (CH_3); 6.77 dd, 1 H, *J* = 2.0 (H-4); 7.35 d, 1 H, *J* = 3.6 (H-3); 7.43 d, 2 H, *J* = 8.64 (H arom.); 7.94 d, 1 H, *J* = 3.0 (H-5); 8.01 d, 2 H (H arom.). IR spectrum: 1 633 (C=N).

2-(4-Chlorophenyl)-5-(2-furyl)-1,3,4-oxadiazole (*IIr*)

Yield 72% (method *A*), m.p. 132 – 133 °C. For $C_{12}H_7ClN_2O_2$ (246.6) calculated: 58.44% C, 2.86% H, 11.36% N; found: 58.73% C, 2.61% H, 11.14% N. ^{1}H NMR spectrum: 6.79 dd, 1 H, J = 2.1 (H-4); 7.38 d, 1 H, J = 3.5 (H-3); 7.65 d, 2 H, J = 8.8 (H arom.); 7.94 d, 1 H, J = 3.5 (H-5); 8.13 d, 2 H (H arom.). IR spectrum: 1 635 (C=N).

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REFERENCES

1. Dodd M. C., Cramer D. L., Ward W. C.: J. Am. Pharm. Assoc. *39*, 313 (1950).
2. Porretta G. C., Scalpo M., Chimenti F., Bolasco A., Biava M.: Il Farmaco, Ed. Sci. *42*, 629 (1987).
3. Frimm R., Kovac J., Zavodska E.: Zb. Pr. CHTF SVST *1967*, 41.
4. Oleinik A. F., Vozyakova T. I., Modnikova G. A., Novickii J. K.: Khim. Geterotsikl. Soedin. *1972*, 1448.
5. Davis C. S., Longhead G. S.: J. Heterocycl. Chem. *4*, 153 (1967).
6. Blomquist A. T., Stevenson H. B.: J. Am. Chem. Soc. *56*, 146 (1934).
7. Frimm R., Kovac S., Kovac J., Bencze K.: Chem. Zvesti *22*, 361 (1968).