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Conversion of 2(*3H*)-Furanones into 1,3,4-Oxadiazoles

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ABSTRACT: *A series of 2-phenyl-5-alkenyl-1,3,4-oxadiazoles were synthesized in high yields from the corresponding dicarbonylhydrazides through cyclodehydration.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:570–574, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10197

INTRODUCTION

2-Aryl-5-alkenyl-1,3,4-oxadiazoles have been reported to show antibacterial [1,2], antifungal [3], analgesic, antiinflammatory [4,5], and hypoglycemic [2] activity. The most popular synthesis of 2,5-disubstituted-1,3,4-oxadiazoles is based on the thermal or acid-catalyzed cyclization of 1,2-diacylhydrazines [6]. Ring closure usually proceeds in the presence of hot phosphorus, using phosphorus oxychloride [2,3,7–10], although an improved method by triphenylphosphine/carbon tetrachloride/triethylamine reagent has also been reported [1]. These results promoted us to convert 2(*3H*)-furanones **1a–f** into 1,3,4-oxadiazoles **4a–f**. In this paper we report selected results of our investigations.

RESULTS AND DISCUSSION

In a previous study, we reported [11,12] the synthesis of 5-aryl-3-arylmethylene-2-(*3H*)-furanones **1a–f** via the condensation reactions of furan-2-carboxaldehyde or 4-dimethylaminobenzaldehyde with 3-aroylpropionic acids under Perkin conditions, which yielded the corresponding *E*-lactones as the only product and with no detectable amount of the *Z*-isomers [7]. This result was consistent with the results reported by Awad et al. [13] and others [14,15] concerning the condensation reaction of 5-methyl-furan-2-carboxaldehyde or 5-methyl thiophene-2-carboxaldehyde with 3-aroylpropionic acids under Perkin conditions. Scheme 1 shows the conversion of **1a–f** into (*E*)-2-aroylmethyl-3-aryl-acrylohydrazides **2a–f**, N^1-(*E*)-2-aroylmethyl-3-aryl-N^2-benzo-acrylohydrazides **3a–f**, 2-phenyl-5-[(*E*)-1-aroylmethyl-2-(2-furyl)vinyl]-1,3,4-oxadiazoles **4a–c**, and 2-phenyl-5-[(*E*)-1-aroylmethyl-2-(4-dimethylaminophenyl)vinyl]-1,3,4-oxadiazoles **4d–f**. Reaction of **2a–c** with benzoyl chloride in dry benzene at refluxing temperature afforded **3a–c** in moderate (52–69%) yield, but the reaction of **2d–f** with benzoyl chloride under the same reaction conditions afforded **3d–f** in low (31–42%) yield.

Treatment of hydrazides **3a–f** with phosphorus oxychloride under reflux furnished **4a–f** in 22–70% yield. The structures of **3a–f** and **4a–f** were determined by spectroscopic methods and analyses. The IR spectral data for compounds **4a–c** are in agreement with our previous data [10].

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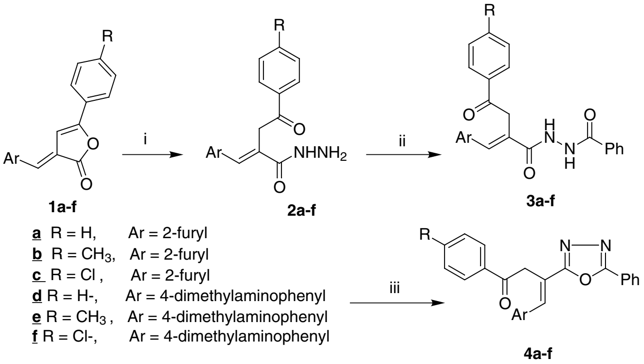
TABLE 1 Optical Properties of **1–4**

	λ_{max} (nm)	*Abso.*		*λ_{max} (nm)*	*Abso.*
1a	404.00	2.340	**3a**	415.00	0.448
	266.00	0.739		341.50	0.383
1b	407.50	1.313		270.00	0.363
	271.00	0.412		227.50	0.081
1c	407.50	0.943	**3b**	417.50	0.244
	311.50	0.053		334.00	0.239
	275.50	0.276		268.00	0.671
	224.50	0.075	**3c**	417.50	0.210
1d	461.00	1.423		340.50	0.181
	320.00	0.208		270.50	0.504
	272.00	0.176	**3d**	455.00	0.921
	218.00	0.098		321.50	0.066
1e	460.50	1.652		271.00	0.362
	320.50	0.252		232.00	−0.093
	305.50	0.264	**3e**	743.00	0.015
	271.00	0.351		455.00	0.755
	212.50	0.168		324.50	0.094
1f	468.50	0.701		273.50	0.363
	324.00	0.327	**3f**	460.50	0.701
	273.00	1.997		273.50	0.327
2a	306.00	0.734		221.50	1.997
2b	306.50	0.778	**4a**	269.50	0.276
	211.00	0.023	**4b**	471.00	0.049
2c	306.50	0.840		276.00	0.349
2d	468.50	0.022	**4c**	466.00	0.067
	353.50	1.044		287.50	0.240
2e	354.00	0.925	**4d**	269.50	0.725
	272.00	0.056		214.00	2.006
2f	473.50	0.003	**4e**	270.00	0.743
	354.50	0.778	**4f**	219.50	1.937

Solvent dichloromethane, $c = 5 \times 10^{-6}$ mol/l for absorption measurements, $c = 1 \times 10^{-6}$ mol/l for emission measurements.

Optical Characterization

The absorption spectra of **1a–f** to **4a–f** were measured in CH_2Cl_2 at a concentration of 5×10^{-6} mol/l. The results obtained are valid for dichloromethane as solvent and we did not find significant altered trends in other solvents. With a view to understand the coplanarity and rotational freedom of individual rings, nonstructured π–π* transition bands have been studied. Compared to parent lactones **1a–c** at absorption maximum $\lambda_{max} = 404$ nm and **1d–f** at $\lambda_{max} = 461$ nm, as outlined in Table 1, the replacement of 2-furyl by 4-dimethylaminophenyl rings, as realized for **1a–c**/**1d–f**, led to a bathochromic shift at the absorption maximum $\Delta\lambda_{max} = +53$–$61$ nm. However, either acrylohydrazides **2a–c** or **2d–f** caused an opposite hypsochromic shift at absorption maximum $\Delta\lambda_{max} = -98$ nm and $\Delta\lambda_{max} = -7$ nm, compared to parent lactones **1a–c** and **1d–f** respectively. Hydrazides **3a–c** caused a bathochromic shift at the absorption maximum $\Delta\lambda_{max} = +10$ nm versus parent lactones **1a–c**, but the hydrazides **3d–f** gave unexpected data for the hypsochromic shift at



SCHEME 1 Reagents and conditions: (i) $NH_2NH_2 \cdot H_2O$/ethanol, stirring at RT for 2 days: (ii) benzoyl chloride in dry benzene heat/3 h: (iii) heating with $POCl_3$ for 1 h.

TABLE 2 Melting Point, Yield, and Elemental Analysis for **1–4**

				Calcd/Found		
	m.p. (°C)	*Yield (%)*	*Formula*	*C*	*H*	*N*
1e	186–188	44.2	$C_{20}H_{19}NO_2$	78.66/78.9	6.27/6.10	4.58/5.00
1f	204–206	52.7	$C_{19}H_{16}ClNO_2$	70.04/70.40	4.95/5.40	4.29/4.90
2d	158–160	77	$C_{19}H_{21}N_3O_2$	70.56/69.90	6.54/6.68	12.99/13.00
2e	134–135	86.7	$C_{19}H_{21}N_3O_2$	71.19/71.00	6.87/6.20	12.45/12.46
2f	126–128	79	$C_{19}H_{20}ClN_3O_2$	63.77/63.70	5.63/5.90	11.74/11.70
3a	167–168	69.4	$C_{22}H_{18}N_2O_4$	70.57/70.10	4.84/4.80	7.84/7.78
3b	170–171	52.6	$C_{23}H_{20}N_2O_4$	71.12/71.00	5.18/5.70	7.21/7.30
3c	253–254	57.1	$C_{22}H_{17}ClN_2O_4$	64.63/64.60	4.19/4.20	6.85/6.71
3d	234–236	31	$C_{26}H_{25}N_3O_3$	73.04/73.04	5.98/6.5	9.82/9.78
3e	247–249	42.3	$C_{27}H_{27}N_3O_3$	73.44/73.8	6.16/6.51	9.51/9.33
3f	266–268	57	$C_{26}H_{24}ClN_3O_3$	67.60/70.00	5.23/5.4	9.09/9.00
4a	83–86	58	$C_{22}H_{16}N_2O_3$	74.14/74.16	4.52/4.60	7.86/7.58
4b	87–90	22	$C_{23}H_{18}N_2O_3$	74.58/74.18	4.89/4.43	7.56/7.28
4c	>360	77	$C_{22}H_{15}ClN_2O_3$	67.61/67.50	3.86/3.70	7.16/7.12
4d	>360	26.6	$C_{26}H_{23}N_3O_2$	76.26/76.14	5.66/5.60	10.26/10.10
4e	>360	14	$C_{27}H_{25}N_3O_2$	76.57/76.34	5.94/5.80	9.92/9.80
4f	>360	65	$C_{26}H_{22}ClN_3O_2$	70.34/70.30	4.99/5.16	9.46/9.40

TABLE 3 Infrared (Nujol) (cm^{-1}) and ^{1}H NMR (Deuteriodimethyl Sulfoxide) Spectral Data for **1–4**

	$\upsilon_{C=O}$, $\upsilon_{C=N}$, υ_{-NH}	$\delta\ ^1H$
1e	1783	2.21 (s, 3H, Ar–C$\underline{H}_3$), 2.96 (s, 6H, –NC$\underline{H}_3$), 6.59 (s, 1H, –CH=C–), 6.69 (d, 2H, *J* = 8.8 Hz, Ar–H), 6.75 (s, 1H, –CH=C–), 7.15 (d, 2H, *J* = 9.05 Hz, Ar–H), 7.62 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.70 (d, 2H, *J* = 8.3 Hz, Ar–H)
1f	1752	2.97 (s, 6H, –NC$\underline{H}_3$), 6.61 (s, 1H, –CH=C–), 6.72 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.17 (d, 2H, *J* = 9.05 Hz, Ar–H), 7.65 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.71 (d, 2H, *J* = 9.05 Hz, Ar–H), 6.77 (s, 1H, –CH=C–)
2d	1648, 1687, 3100–3300	2.84 (s, 6H, –NC$\underline{H}_3$), 2.98 (d, 1H, *J* = 2.4 Hz, –NHN$\underline{H_2a}$), 3.08 (d, 1H, *J* = 2 Hz, –NHN$\underline{H_2b}$), 4.24 (s, 2H, –CH$_2$), 6.47 (s, 1H, –CH=C–), 6.62 (d, 2H, *J* = 8.9 Hz, Ar–H), 7.07 (t, 1H, *J* = 2.3 Hz, CO-N$\underline{H}$NH$_2$), 7.17–7.29 (m, 5H, Ph-H), 7.24 (d, 2H, *J* = 8.9 Hz, Ar–H)
2e	1652–1692, 3100–3300	2.21 (s, 3H, Ar–C$\underline{H}_3$), 2.96 (s, 6H, –NC$\underline{H}_3$), 3.12 (d, 2H, *J* = 2.4 Hz, –NHN$\underline{H_2b}$), 4.33 (s, 2H, –CH$_2$), 6.58 (s, 1H, –CH=C–), 6.69 (d, 2H, *J* = 8.7 Hz, Ar–H), 7.15 (t, 1H, *J* = 2.3 Hz, CO-N$\underline{H}$NH$_2$), 7.33 (d, 2H, *J* = 8.7 Hz, Ar–H), 7.62 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.70 (d, 2H, *J* = 8.3 Hz, Ar–H)
2f	1653–1697, 3110–3330	2.92 (s, 6H, –NC$\underline{H}_3$), 3.08 (d, 1H, *J* = 2.4 Hz, –NHN$\underline{H_2a}$), 3.15 (d, 1H, *J* = 2.4 Hz, –NHN$\underline{H_2b}$), 4.34 (s, 2H, –CH$_2$), 6.63 (s, 1H, –CH=C–), 6.68 (d, 2H, *J* = 6.7 Hz, Ar–H), 7.15 (t, 1H, *J* = 2.3 Hz, CO-N$\underline{H}$NH$_2$), 7.33 (d, 2H, *J* = 6.7 Hz, Ar–H), 7.35–7.41 (m, 4H, Cl–Ar–H)
3a	1667–1725, 3112–3263	3.85 (s, 2H, C$\underline{H}_2$CO–), 6.63 (dd, 1H, *J* = 1.8, 3.3 Hz, furan-H4), 7.04 (d, 1H, *J* = 3 Hz, furan-H3), 6.75 (s, 1H, furan-CH=C–), 7.37–7.43 (m, 5H, Ph-H), 7.64 (d, 1H, *J* = 1.8 Hz, furan-H5), 7.75 (m, 5H, Ar–H), 9.30 (s, 1H, –NH-NH–), 10.67 (s, 1H, –NH-NH–)
3b	1667–1699, 1726, 3099–3267	2.21 (s, 3H, Ar–C$\underline{H}_3$), 3.88 (s, 2H, C$\underline{H}_2$CO), 6.70 (s, 1H, furan-CH=C–), 6.87 (d, 2H, *J* = 9 Hz, Ar–H), 7.00 (d, 1H, *J* = 3.6 Hz, furan-H3), 7.14 (dd, 1H, *J* = 1.8, 3.6 Hz, furan-H4), 7.45 (d, 2H, *J* = 9 Hz, Ar–H), 7.69 (d, 2H, *J* = 7.5 Hz, Ar–H), 7.96 (d, *J* = 1.5 Hz, furan-H5), 8.34 (s, 1H, –NH-NH–), 11.01 (s, 1H, –NH-NH–)
3c	1660–1726, 3225–3316	3.86 (s, 2H, C$\underline{H}_2$CO), 6.61 (s, 1H, furan-CH=C–), 6.85 (d, 2H, *J* = 9 Hz, Ar–H), 7.1 (d, 1H, *J* = 3.6 Hz, furan-H3), 7.2 (dd, 1H, *J* = 1.8, 3.6 Hz, furan-H4), 7.38 (d, 2H, *J* = 8.1 Hz, Ar–H), 7.42 (d, 2H, *J* = 9 Hz, Ar–H), 7.73 (d, 2H, *J* = 7.5 Hz, Ar–H), 7.85 (s, 1H, –NH-NH–), 7.97 (d, 1H, *J* = 1.5 Hz, furan-H5), 8.57 (s, 1H, –NH–), 10.72 (s, 1H, –NH–)
3d	1665–1726, 3230–3318	3.03 (s, 6H, –NC$\underline{H}_3$), 3.86 (s, 2H, C$\underline{H}_2$CO–), 6.75 (s, 1H, –CH=C–), 6.80 (d, 2H, *J* = 8.9 Hz, Ar–H), 7.32–7.84 (m, 10H, Ph-H), 7.75–7.32 (d, 2H, *J* = 9 Hz, Ar–H), 9.30 (s, 1H, –NH-NH–), 11.16 (s, 1H, –NH-NH–)
3e	1661–1729, 3232–3320	2.21 (s, 3H, CH$_3$), 2.98 (s, 6H, –NC$\underline{H}_3$), 3.56 (s, 2H, C$\underline{H}_2$CO–), 6.59 (s, 1H, –CH=C–), 6.72 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.15 (d, 2H, *J* = 9.05 Hz, Ar–H), 7.39–7.53 (m, 5H, Ph-H), 7.64–7.62 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.77–7.75 (d, 2H, *J* = 8.8 Hz, Ar–H), 8.34 (s, 1H, –NH-NH–), 11.04 (s, 1H, –NH-NH–)
3f	1663–1727, 3224–3330	2.98 (s, 6H, –NC$\underline{H}_3$), 3.56 (s, 2H, C$\underline{H}_2$CO–), 6.81 (s, 1H, –CH=C–), 6.74 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.15 (d, 2H, *J* = 9.05 Hz, Ar–H), 7.52 (m, 5H, Ph-H), 7.65 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.78 (d, 2H, *J* = 8.8 Hz, Ar–H), 8.4 (s, 1H, –NH-NH–), 11.4 (s, 1H,–NH-NH–)
4a	1689, 1590–1620, 3217	4.34 (s, 2H, –C$\underline{H}_2$–), 6.09 (s, 1H, furan-CH=C–), 6.66 (dd, 1H, *J* = 1.8, 3.3 Hz, furan-H4), 7.15 (d, 1H, *J* = 3.3 Hz, furan-H3), 7.07–7.64 (m, 10H, Ph-H), 7.95 (d, *J* = 1.5 Hz, furan-H5)
4b	1690, 1590–1616, 3217	2.34 (s, 3H, Ar–C$\underline{H}_3$), 4.58 (s, 2H, –C$\underline{H}_2$), 6.09 (s, 1H, –CH=C–), 7.07 (dd, 1H, *J* = 1.8, 3.6 Hz, furan-H4), 7.20 (d, 1H, *J* = 3.3 Hz, furan-H3), 7.38 (d, 2H, *J* = 8.7, Ar–H), 7.45 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.48–7.85 (m, 5H, Ph-H), 8.20 (d, 1H, *J* = 1.5 Hz, furan-H5)
4c	1689, 1591–1619, 3219	4.44 (s, 2H, –C$\underline{H}_2$), 6.71 (dd, 1H, *J* = 1.8, 3.3 Hz, furan-H4), 7.13 (s, 1H, CH=C–), 7.18 (d, 1H, *J* = 3.3 Hz, furan-H3), 7.38 (d, 2H, *J* = 8.7 Hz, Ar–H), 7.39–7.68 (m, 5H, Ph-H), 7.70 (d, 2H, *J* = 8.7 Hz, Ar–H), 7.95 (d, 1H, *J* = 1.5 Hz, furan-H5)
4d	1692, 1592–1622, 3221	2.98 (s, 6H, –NC$\underline{H}_3$), 4.1 (s, 2H, C$\underline{H}_2$CO–), 6.75 (s, 1H, –CH=C–), 6.80 (d, 2H, *J* = 8.9 Hz, Ar–H), 7.32–7.84 (m, 10H, Ph-H), 7.75–7.32 (d, 2H, *J* = 9 Hz, Ar–H)
4e	1695, 1595–1618, 3222	2.21 (s, 3H, CH$_3$), 2.98 (s, 6H, –NC$\underline{H}_3$), 3.56 (s, 2H, C$\underline{H}_2$CO–), 6.59 (s, 1H, –CH=C–), 6.72 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.15 (d, 2H, *J* = 9.05 Hz, Ar–H), 7.39–7.53 (m, 5H, Ph-H), 7.64–7.62 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.77–7.75 (d, 2H, *J* = 8.8 Hz, Ar–H)
4f	1690, 1590–1624, 3230	2.99 (s, 6H, –NC$\underline{H}_3$), 4.03 (s, 2H, –C$\underline{H}_2$CO), 7.72 (s, 1H, CH=C–), 6.82 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.32 (d, 2H, *J* = 8.7 Hz, Ar–H), 7.47 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.54–7.73 (m, 5H, Ph-H), 7.92 (d, 2H, *J* = 8.7 Hz, Ar–H)

absorption maximum $\Delta\lambda_{max} = -6$ nm compared to the parent lactones **1d–f**. The parent lactones **1a–f**, hydrazides **2a–f** and/or **3a–f**, in which one lactone ring was replaced by hydrazides **2a–f** or **3a–f** and/or 1,3,5-oxadiazole **4a–f** moiety, are compared; only the introduction of a second 1,3,5-oxadiazole unit led to a further significant hypsochromic shift of **4a–c** at absorption maximum $\Delta\lambda_{max} = -130$ nm and of **4d–f** at $\Delta\lambda_{max} = -191$ nm. These results are in agreement with a theoretically calculated convergence of the frontier orbitals.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Plus 300 (300 MHz) or Bruker XL 300 (300 MHz) instrument. Infrared spectra were taken on a Perkin-Elmer 1600 FT-IR spectrometer. Mass points were recorded on a Kratos Concept instrument. Melting points were measured on an electrothermal digital melting point apparatus and are uncorrected. The R_f values reported for TLC analyses were determined on Macherey–Nagel 0.25-mm layer fluorescent UV$_{254}$ plates with the indicated solvent system. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ) at Murcia University, Spain, and Cairo University.

(3E)-3-Arylmethylene-5-arylfuran-2(3H)-ones **1a–f**

These were prepared by following the literature method [7,8,12,16,17].

(E)-2-Aroylmethyl-3-(2-aryl)acrylohydrazides **2a–f**

These were prepared by following the literature method reported [7,8,12]. To a suspension of **1a–f** (2 mmol) in ethanol (5 ml) under nitrogen atmosphere at 25°C, hydrazine hydrate (3 mmol) was added and the mixture was stirred at 25°C for 12 h. The solvent was evaporated in vacuo, and the solid residue was recrystallized from ethanol to give **2a–f**. Analytical data are given in Tables 2 and 3.

N-(2E)-3-Substituted-2-(2-oxosubstituted-ethyl)prop-2-enoylbenzohydrazides **3a–f**

To a suspension of **2a–f** (2 mmol) in dry benzene (15 ml) at 25°C, benzoyl chloride (2.1 mmol) was added and the mixture was heated under reflux at 75°C for 6 h. The solvent was evaporated in vacuo, and the solid residue was recrystallized from ethanol to give **3a–f**. Analytical data are given in Tables 2 and 3.

(3E)-1,4-Diaryl-3(5-phenyl)-1,3,4-oxadiazol-2-yl-but-3-en-1-ones **4a–f**

A mixture of **3a–f** (2 mmol) and phosphorus oxychloride (10 ml) was refluxed for 1 h. The mixture was cooled, poured onto crushed ice (20 ml), and then neutralized with 1.0 N aqueous solution of sodium hydrogen carbonate. The yellowish precipitate was collected by filtration, washed with water, and recrystallized from acetonitrile to give **4a–f**. Analytical data are given in Tables 2 and 3.

CONCLUSION

We have demonstrated the benzoylation of (*E*)-2-aroylmethyl-3-(2-aryl) acrylohydrazides **2a–f** in nonpolar solvent by benzoyl chloride and cyclodehydration of *N*-(2*E*)-3-substituted-2-(2-oxo-substitute-ethyl)prop-2-enoylbenzohydrazides **3a–f** by phosphorus oxychloride to give (3*E*)-1,4-disubstituted-3(5-phenyl-1,3,4-oxadiazol-2-yl)but-3-ene-1-ones **4a–f**.

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