

Novel Synthesis of *N*-{6-Aryl-4-[(*E*)-2-furylmethylene]-1,2,3,4-tetrahydro-3-oxopyridazin-1-ylcarbonyl}-*p*-toluenesulfonamides and *N*-{5-[(*E*)-1-Aroylmethyl-2-(2-furyl) vinyl]-1,3,4-oxadiazol-2-yl}-*p*-toluenesulfonamides

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Novel *N*-{6-aryl-4-[(*E*)-2-furylmethylene]-1,2,3,4-tetrahydro-3-oxopyridazin-1-ylcarbonyl}-*p*-toluenesulfonamides **4a-d** were prepared by the reaction of (*E*)-2-aroymethyl-3-(2-furyl) acrylohydrazides **2a-d** with tosylisocyanate. This has been shown to occur by initial formation of (*E*)-2-aroymethyl-3-(2-furyl)-*N'*-(tosylaminocarbonyl) acrylohydrazides **3a-d** followed by acid catalyzed cyclization to afford *N*-{5-[(*E*)-1-aroymethyl-2-(2-furyl)vinyl]-1,3,4-oxadiazol-2-yl}-*p*-toluenesulfonamides **5a-d**.

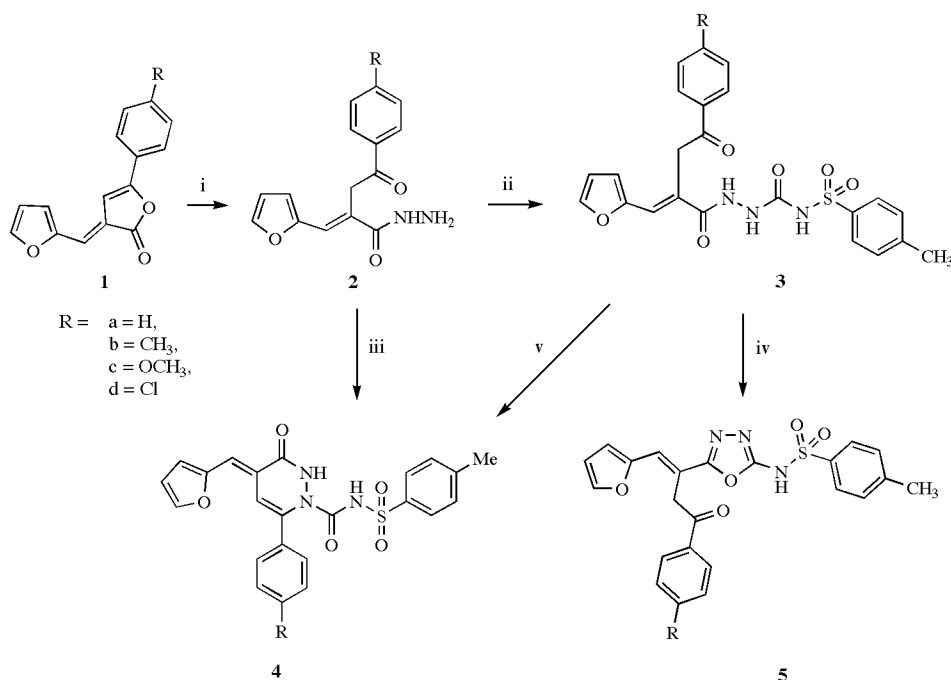
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Introduction.

In connection with our synthetic approach to the 5-aryl-3-[(*E*)-2-furylmethylene]furan-2(3*H*)-ones **1a-d** [1-4], these compounds were isolated in almost quantitative yield upon condensation reaction of furan-2-carboxaldehyde with 3-aroymethylpropionic acids under Perkin conditions yielding the *E*-lactones as the only product and there is no detectable amount of the *Z*-isomers by ¹H NMR [5]. 2(3*H*)-Furanones **1a-d** react with hydrazine hydrate in ethanol to give (*E*)-2-aroymethyl-3-(2-furyl)acrylohydrazides **2a-d**, which were found to be useful precursors in the synthesis of several heterocyclic compounds [4].

Conversion of the 2(3*H*)-furanones **1a-d** into the corresponding 3(2*H*)-pyridazones **4a-d** and oxadiazoles **5a-d** are of potential biological interest [6-10]. Usually, 3(2*H*)-pyridazinones are prepared from β-oxoalkanoic acid derivatives and hydrazines [11] and 1,3,4-oxadiazoles are prepared from 1,2-diacylhydrazines [12]. We report here the preparation of (*E*)-2-aroymethyl-3-(2-furyl)-*N'*-(tosylaminocarbonyl)acrylohydrazides **3a-d**, which, upon acid catalyzed cyclization, furnished *N*-{6-aryl-4-[(*E*)-2-furylmethylene]-1,2,3,4-tetrahydro-3-oxopyridazin-1-yl carbonyl}-*p*-toluenesulfonamides **4a-d** and *N*-{5-[(*E*)-1-aroymethyl-2-(2-furyl)vinyl]-1,3,4-oxadiazol-2-yl}-*p*-toluenesulfonamides **5a-d**.

Scheme 1



Reagents and conditions; i) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ /ethanol, stirring at RT for 2 days; ii) Stirring with tosylisocyanate in acetonitrile at 0-5 °C for 12 hrs; iii) Stirring with tosylisocyanate in acetonitrile at 25 °C for 2 days. iv) Refluxing with POCl_3 for 20 min; v) Stirring with 1.0 *N* HCl in acetonitrile for 1 h.

Results and Discussion.

Reaction of (*E*)-2-aroylemethyl-3-(2-furyl)acrylohy-drazides **2a-d** with tosylisocyanate at 0–25 °C gave (*E*)-2-aroylemethyl-3-(2-furyl)-*N'*-(tosylaminocarbonyl) acrylohy-drazides **3a-d**, and *N*-{6-aryl-4-[(*E*)-2-furylmethyl-ene]-1,2,3,4-tetrahydro-3-oxopyridazin-1-ylcarbonyl}-*p*-toluenesulfonamides **4a-d**. Formation of product **3a-d** and **4a-d** was dependent on the reaction conditions. When the reaction was carried out at 0–5 °C for 12 h, (*E*)-2-aroylemethyl-3-(2-furyl)-*N'*-(tosylaminocarbonyl)-acrylohy-drazides **3a-d** were obtained in 31–45% yield. However, treatment of **2a-d** with tosylisocyanate at 25 °C for 48 h gave *N*-{6-aryl-4-[(*E*)-2-furylmethylene]-1,2,3,4-tetrahydro-3-oxopyridazin-1-yl carbonyl}-*p*-toluenesulfonamides **4a-d** in 75–82% yield. 3(2*H*)-Pyridazinones **4a-d** were also obtained by cyclization of hydrazides **3a-d** in a mixture of acetonitrile and 1 *N* hydrochloric acid. Treatment of hydrazides **3a-d** with phosphorus oxychloride under reflux furnished the corresponding *N*-{5-[(*E*)-1-aroylemethyl-2-(2-furyl)vinyl]-1,3,4-oxadiazol-2-yl}-*p*-toluenesulfonamides **5a-d** in 75–81% yield as shown in Scheme 1.

The structures of novel compounds **3-5** were determined by spectroscopic methods and analyses for C, H, N and S. The IR spectral data for compounds **4b,d** are in agreement with the data of related 1-benzoyl-6-aryl-4-thienylidene-1,6-dihydropyridazin-3-(2*H*)ones [13].

Conclusion.

N-{6-aryl-4-[(*E*)-2-furylmethylene]-1,2,3,4-tetrahydro-3-oxopyridazin-1-ylcarbonyl}-*p*-toluenesulfonamides **4a-d** and *N*-{5-[(*E*)-1-aroylemethyl-2-(2-furyl)vinyl]-1,3,4-oxadiazol-2-yl}-*p*-toluenesulfonamides **5a-d** were prepared in one step by acid catalyzed cyclization of (*E*)-2-aroylemethyl-3-(2-furyl)-*N'*-(tosylaminocarbonyl) acrylohy-drazides **3a-d** in good yields.

EXPERIMENTAL

¹H NMR spectra were recorded on Varian Plus 300 (300 MHz) or Bruker XL 300 (300 MHz) instruments, the ¹³C NMR spectra (with DEPT 135) on a Bruker WP80 or XL 300 instrument. Infrared Red 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 UV₂₅₄ plates with the indicated solvent system. M-H-W Laboratories (Phoenix, AZ) performed elemental analyses.

(*E*)-2-Aroylemethyl-3-(2-furyl)-*N'*-(tosylaminocarbonyl)acrylohy-drazides **3a-d**.

General Procedure A.

To a suspension of (*E*)-2-aroylemethyl-3-(2-furyl)acrylohy-drazides **2a-b** (2 mmoles) in acetonitrile (2 ml) under a nitrogen atmosphere at 0–5°, *p*-toluenesulfonyl isocyanate (0.3 ml, 2.1 mmoles) was added and the mixture was stirred at 0–5° for 12 hours. The precipitate was collected by filtration to give **3a-d**. Analytical data for compounds **3a-d** are given in Tables 1 and 2.

N-{6-Aryl-4-[(*E*)-2-furylmethylene]-1,2,3,4-tetrahydro-3-oxopyridazin-1-ylcarbonyl}-*p*-toluenesulfonamides **4a-d**.

General Procedure B.

To a suspension of (*E*)-2-aroylemethyl-3-(2-furyl)acrylohy-drazides **2a-d** (2 mmoles) in acetonitrile (2 ml) under nitrogen atmosphere at 0–5°, *p*-toluenesulfonylisocyanate (0.3 ml, 2.1 mmoles) was added and the mixture was stirred at 0–5° for 12 hours and then at 25° for 48 hours. The solvent was evaporated *in vacuo*, and the solid residue was recrystallized from ethanol to give **4a-d**.

General Procedure C.

To a suspension of (*E*)-2-aroylemethyl-3-(2-furyl)-*N'*-(tosylaminocarbonyl)acrylohy-drazides **3a-d** (1 mmole) in acetonitrile (4 ml), 1.0 *N* hydrochloric acid (1 ml) was added and the mixture was stirred at 25° for one hour. The solvent was evaporated *in vacuo* and the solid residue was recrystallized from ethanol to give **4a-d**. Analytical data for compounds **4a-d** are given in Tables 1, 2.

Table 1
Physical and Elemental Analytical Data for Compounds **3-5**

No.	Alkyl group	mp °C(Solvent)	Yield%	Formula	[Cald./found]			
					C	H	N	S
3a	H	110-112 (Acetonitrile)	45	C ₂₃ H ₂₁ N ₃ O ₆ S	59.09/59.05	4.52/4.62	8.98/8.78	6.85/6.73
3b	CH ₃	133-135 (Acetonitrile)	32	C ₂₄ H ₂₃ N ₃ O ₆ S	59.98/59.86	4.82/4.85	8.74/8.74	6.67/6.68
3c	OCH ₃	125-127 (Acetonitrile)	31	C ₂₄ H ₂₃ N ₃ O ₇ S	58.05/58.01	4.66/4.65	8.46/8.57	6.45/6.77
3d	Cl	190-192 (Acetonitrile)	34	C ₂₃ H ₂₀ ClN ₃ O ₆ S	55.03/55.15	4.01/3.99	8.37/8.36	6.38/6.42
4a	H	156-158 (Ethanol)	75	C ₂₃ H ₁₉ N ₃ O ₅ S	61.45/61.55	4.26/4.16	9.34/9.28	7.13/7.33
4b	CH ₃	175-177 (Ethanol)	82	C ₂₄ H ₂₁ N ₃ O ₅ S	62.19/62.18	4.56/4.55	9.06/9.09	6.91/6.89
4c	OCH ₃	168-170 (Ethanol)	82	C ₂₄ H ₂₁ N ₃ O ₆ S	60.11/60.15	4.41/4.45	8.76/8.76	6.68/6.77
4d	Cl	185-186 (Ethanol)	77	C ₂₃ H ₁₈ ClN ₃ O ₅ S	57.08/57.05	3.74/3.73	8.68/8.66	6.62/6.62
5a	H	145-147 (Acetonitrile)	75	C ₂₃ H ₁₉ N ₃ O ₅ S	61.45/61.55	4.26/4.16	9.34/9.28	7.13/7.33
5b	CH ₃	176-177 (Acetonitrile)	80	C ₂₄ H ₂₁ N ₃ O ₅ S	62.19/62.18	4.56/4.55	9.06/9.09	6.91/6.89
5c	OCH ₃	178-180 (Acetonitrile)	81	C ₂₄ H ₂₁ N ₃ O ₆ S	60.11/60.15	4.41/4.45	8.76/8.76	6.68/6.77
5d	Cl	166-168 (Acetonitrile)	75	C ₂₃ H ₁₈ ClN ₃ O ₅ S	57.08/57.05	3.74/3.73	8.68/8.66	6.62/6.62

Table 2
Infrared (IR) and ¹H NMR (300 MHz) spectral Data for Compounds 3-5

Cpd.No	Alkyl group	(IR) ν_{max} (Nujol)/cm ⁻¹ $\nu_{\text{C=O}}$; $\nu_{\text{C=N}}$; ν_{NH}	¹ H NMR [deuteriodimethyl sulfoxide]
3a	H	1667(s), 1725(w), 3112(w), 3263.6(s)	d = 2.36 (s, 3H, Ar-CH ₃), 3.85 (s, 2H, CH ₂ COPh), 6.63 (dd, 1H, <i>J</i> = 1.8, 3.3 Hz, Furan-H4), 7.04 (d, 1H, <i>J</i> = 3 Hz, Furan-H3), 6.75 (s, 1H, furan-CH=C-), 7.35 (d, 2H, <i>J</i> = 8.4 Hz, Ar-H), 7.37-7.43 (m, 5H, Ph-H), 7.64 (d, <i>J</i> = 1.8 Hz, Furan-H5), 7.75 (d, 2H, <i>J</i> = 8.1 Hz, Ar-H), 9.30 (s, 1H, -NH-NH-), 10.67 (s, 1H, -NH-NH-), 11.63 (s, 1H, -CONHSO ₂ -Ar) ppm.
3b	CH ₃	1667(s), 1699, 1725.8(w), 3099(w), 3266.6(S)	d = 2.36 (s, 3H, Ar-CH ₃), 2.37 (s, 3H, Ar-CH ₃), 3.88 (s, 2H, CH ₂ COAr), 6.70 (s, 1H, furan-CH=C-), 6.87 (d, 2H, <i>J</i> = 9 Hz, Ar-H), 7.00 (d, 1H, <i>J</i> = 3.6 Hz, Furan-H3), 7.14 (dd, 1H, <i>J</i> = 1.8, 3.6 Hz, Furan-H4), 7.32 (d, 2H, <i>J</i> = 8.1 Hz, Ar-H), 7.45 (d, 2H, <i>J</i> = 9 Hz, Ar-H), 7.69 (d, 2H, <i>J</i> = 7.5 Hz, Ar-H), 7.82 (s, 1H, -NH-NH-), 7.96 (d, <i>J</i> = 1.5 Hz, Furan-H5), 8.28 (s, 1H, -NH-NH-), 10.68 (s, 1H, -CONHSO ₂ -Ar) ppm.
3c	OCH ₃	1651(s), 1680(s), 1737(w), 3214(s), 3376(w)	d = 2.44 (s, 3H, Ar-CH ₃), 3.80 (s, 3H, Ar-OCH ₃), 3.85 (s, 2H, CH ₂ COAr), 6.75 (d, 1H, <i>J</i> = 3 Hz, furan-CH=C-), 6.85 (d, 2H, <i>J</i> = 9 Hz, Ar-H), 7.05 (d, 1H, <i>J</i> = 3.6 Hz, Furan-H3), 7.12 (dd, 1H, <i>J</i> = 1.8, 3.6 Hz, Furan-H4), 7.37 (d, 2H, <i>J</i> = 8.1 Hz, Ar-H), 7.41 (d, 2H, <i>J</i> = 9 Hz, Ar-H), 7.71 (d, 2H, <i>J</i> = 7.5 Hz, Ar-H), 7.81 (s, 1H, -NH-NH-), 7.95 (d, <i>J</i> = 1.5 Hz, Furan-H5), 8.27 (s, 1H, -NH-NH-), 10.68 (s, 1H, -CONHSO ₂ -Ar) ppm.
3d	Cl	1663(s), 1702(s), 1726(w), 3233(s), 3316(w)	d = 2.38 (s, 3H, Ar-CH ₃), 3.79 (s, 2H, CH ₂ COAr), 6.61 (s, 1H, furan-CH=C-), 6.85 (d, 2H, <i>J</i> = 9 Hz, Ar-H), 7.1 (d, 1H, <i>J</i> = 3.6 Hz, Furan-H3), 7.2 (dd, 1H, <i>J</i> = 1.8, 3.6 Hz, Furan-H4), 7.38 (d, 2H, <i>J</i> = 8.1 Hz, Ar-H), 7.42 (d, 2H, <i>J</i> = 9 Hz, Ar-H), 7.73 (d, 2H, <i>J</i> = 7.5 Hz, Ar-H), 7.85 (s, 1H, -NH-NH-), 7.97 (d, <i>J</i> = 1.5 Hz, Furan-H5), 8.57 (s, 1H, -NH-NH-), 10.72 (s, 1H, -CONHSO ₂ -Ar) ppm.
4a	H	1662(s), 1699(w), 3112(w), 3263.6(s)	d = 2.38 (s, 3H, Ar-CH ₃), 6.55 (s, 1H, -CH=C-Ar), 6.70 (dd, 1H, <i>J</i> = 1.8, 3.3 Hz, Furan-H4), 7.06 (s, 1H, furan-CH=C-), 7.15 (d, 1H, <i>J</i> = 3.3 Hz, Furan-H3), 7.30-7.42 (m, 5H, Ph-H), 7.46 (d, 2H, <i>J</i> = 8.4 Hz, Ar-H), 7.69 (d, 2H, <i>J</i> = 8.1 Hz, Ar-H), 7.95 (d, <i>J</i> = 1.5 Hz, Furan-H5), 9.32 (s, 1H, NH), 11.49 (s, 1H, -CONHSO ₂ -Ar) ppm.
4b	CH ₃	1668(s), 1725.8(w), 3099(w), 3266.6(S)	d = 2.35 (s, 3H, Ar-CH ₃), 2.38 (s, 3H, Ar-CH ₃), 6.48 (s, 1H, -CH=C-Ar), 6.71 (dd, 1H, <i>J</i> = 1.8, 3.6 Hz, Furan-H4), 6.85 (d, 2H, <i>J</i> = 8.7 Hz, Ar-H), 6.98 (s, 1H, furan-CH=C-), 7.18 (d, 1H, <i>J</i> = 3.6 Hz, furan-H3), 7.36 (d, 2H, <i>J</i> = 8.4, Ar-H), 7.42 (d, 2H, <i>J</i> = 8.7 Hz, Ar-H), 7.68 (d, 2H, <i>J</i> = 8.4 Hz, Ar-H), 7.92 (d, <i>J</i> = 1.5 Hz, furan-H5), 8.32 (s, 1H, NH), 10.49 (s, 1H, -CONHSO ₂ -Ar) ppm.
4c	OCH ₃	1679(s), 1737(w), 3214(s), 3376(w)	d = 2.36 (s, 3H, Ar-CH ₃), 3.78 (s, 3H, Ar-OCH ₃), 6.46 (s, 1H, -CH=C-Ar), 6.68 (dd, 1H, <i>J</i> = 1.8, 3.3 Hz, Furan-H4), 6.86 (d, 2H, <i>J</i> = 8.7 Hz, Ar-H), 6.99 (s, 1H, furan-CH=C-), 7.1 (d, 1H, <i>J</i> = 3.3 Hz, furan-H3), 7.35 (d, 2H, <i>J</i> = 8.4 Hz, Ar-H), 7.42 (d, 2H, <i>J</i> = 9 Hz, Ar-H), 7.69 (d, 2H, <i>J</i> = 8.4 Hz, Ar-H), 7.92 (d, <i>J</i> = 1.5 Hz, furan-H5), 8.27 (s, 1H, NH), 10.67 (s, 1H, -CONHSO ₂ -Ar) ppm.
4d	Cl	1665(s), 1728(w), 3233(s), 3316(w)	d = 2.38 (s, 3H, Ar-CH ₃), 6.54 (s, 1H, -CH=C-Ar), 6.71 (dd, 1H, <i>J</i> = 1.8, 3.3 Hz, Furan-H4), 6.87 (d, 2H, <i>J</i> = 8.4 Hz, Ar-H), 7.1 (s, 1H, furan-CH=C-), 7.18 (d, 1H, <i>J</i> = 3.3 Hz, furan-H3), 7.37 (d, 2H, <i>J</i> = 8.7 Hz, Ar-H), 7.47 (d, 2H, <i>J</i> = 8.4 Hz, Ar-H), 7.69 (d, 2H, <i>J</i> = 8.1 Hz, Ar-H), 7.95 (d, <i>J</i> = 1.5 Hz, Furan-H5), 9.34 (s, 1H, NH), 10.86 (s, 1H, -CONHSO ₂ -Ar) ppm.
5a	H	1698.2(s), 1578-1615, 3263	d = 2.38 (s, 3H, Ar-CH ₃), 4.36 (s, 2H, -CH ₂ COPh), 6.66 (dd, 1H, <i>J</i> = 1.8, 3.3 Hz, Furan-H4), 7.1 (s, 1H, furan-CH=C-), 7.15 (d, 1H, <i>J</i> = 3.3 Hz, Furan-H3), 7.35-7.46 (m, 5H, Ph-H), 7.48 (d, 2H, <i>J</i> = 8.4 Hz, Ar-H), 7.69 (d, 2H, <i>J</i> = 8.4 Hz, Ar-H), 7.95 (d, <i>J</i> = 1.5 Hz, Furan-H5), 11.49 (s, 1H, -CONHSO ₂ -Ar) ppm.
5b	CH ₃	1692(s), 1587-1613, 3216(s)	d = 2.35 (s, 3H, Ar-CH ₃), 2.38 (s, 3H, Ar-CH ₃), 4.36 (s, 2H, -CH ₂ COAr), 6.67 (dd, 1H, <i>J</i> = 1.8, 3.6 Hz, Furan-H4), 6.82 (d, 2H, <i>J</i> = 8.4 Hz, Ar-H), 6.98 (s, 1H, furan-CH=C-), 7.17 (d, 1H, <i>J</i> = 3.3 Hz, furan-H3), 7.35 (d, 2H, <i>J</i> = 8.7, Ar-H), 7.44 (d, 2H, <i>J</i> = 8.4 Hz, Ar-H), 7.67 (d, 2H, <i>J</i> = 8.7 Hz, Ar-H), 7.93 (d, <i>J</i> = 1.5 Hz, furan-H5), 10.49 (s, 1H, -CONHSO ₂ -Ar) ppm.
5c	OCH ₃	1692(s), 1589-1610, 3220(s)	d = 2.38 (s, 3H, Ar-CH ₃), 3.81 (s, 3H, Ar-OCH ₃), 4.47 (s, 2H, -CH ₂ COAr), 6.71 (dd, 1H, <i>J</i> = 1.8, 3.3 Hz, Furan-H4), 6.87 (d, 2H, <i>J</i> = 8.4 Hz, Ar-H), 7.1 (s, 1H, furan-CH=C-), 7.18 (d, 1H, <i>J</i> = 3.3 Hz, Furan-H3), 7.37 (d, 2H, <i>J</i> = 8.7 Hz, Ar-H), 7.47 (d, 2H, <i>J</i> = 8.4 Hz, Ar-H), 7.69 (d, 2H, <i>J</i> = 8.7 Hz, Ar-H), 7.95 (d, <i>J</i> = 1.5 Hz, Furan-H5), 10.86 (s, 1H, -CONHSO ₂ -Ar) ppm.
5d	Cl	1689(s), 1590-1620, 3217(s)	d = 2.38 (s, 3H, Ar-CH ₃), 4.47 (s, 2H, -CH ₂ COAr), 6.71 (dd, 1H, <i>J</i> = 1.8, 3.3 Hz, Furan-H4), 6.87 (d, 2H, <i>J</i> = 8.4 Hz, Ar-H), 7.1 (s, 1H, furan-CH=C-), 7.18 (d, 1H, <i>J</i> = 3.3 Hz, Furan-H3), 7.37 (d, 2H, <i>J</i> = 8.7 Hz, Ar-H), 7.47 (d, 2H, <i>J</i> = 8.4 Hz, Ar-H), 7.69 (d, 2H, <i>J</i> = 8.7 Hz, Ar-H), 7.95 (d, <i>J</i> = 1.5 Hz, Furan-H5), 10.86 (s, 1H, -CONHSO ₂ -Ar) ppm.

N-{5-[(*E*)-1-Aroylmethyl-2-(2-furyl)vinyl]-1,3,4-oxadiazol-2-yl}-*p*-toluenesulfonamides **5a-d**.

General Procedure D.

A mixture of (*E*)-2-aroylmethyl-3-(2-furyl)-*N*²-(tosylaminocarbonyl)acrylohydrazides **3a-d** (2 mmoles) and phospho-

rus oxychloride (10 ml) was refluxed for one hour. The mixture was cooled, poured onto crushed ice (20 ml), neutralized with 1.0 *N* aqueous solution of sodium hydrogencarbonate. The yellowish precipitate was collected by filtration, washed with water and recrystallized from acetonitrile to give **5a-d**. Analytical data for compounds **5a-d** are given in Tables 1, 2.

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