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### NEW SYNTHESSES OF SUBSTITUTED PYRIDAZIN-6-ONES AND PYRIDAZIN-6-IMINES

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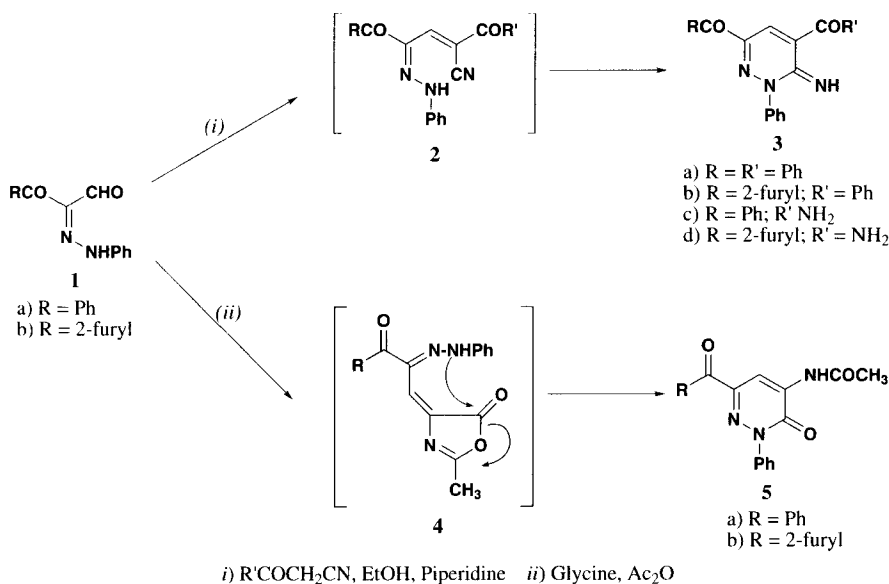


## NEW SYNTHESIS OF SUBSTITUTED PYRIDAZIN-6-ONES AND PYRIDAZIN-6-IMINES

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The biological and medicinal activity of pyridazines<sup>1,2</sup> has stimulated considerable interest in the chemistry of this ring system.<sup>3,4</sup> We have developed several novel and efficient syntheses of pyridazine derivatives from the readily obtainable 2-arylhydrazonoketones,<sup>5-8</sup> 2-arylhydrazononitriles<sup>9,10</sup> and 2-arylhydrazonoaldehydes.<sup>11</sup> In conjunction with this work, we now report the synthesis of new, otherwise not readily obtainable pyridazinones needed for the evaluation of their potential as new biodegradable agrochemicals. The present work has also resulted in the development of new syntheses of 3-aro-yl- and 3-heteroaro-yl-5-substituted pyridazin-6-ones for which no other alternate syntheses are available.

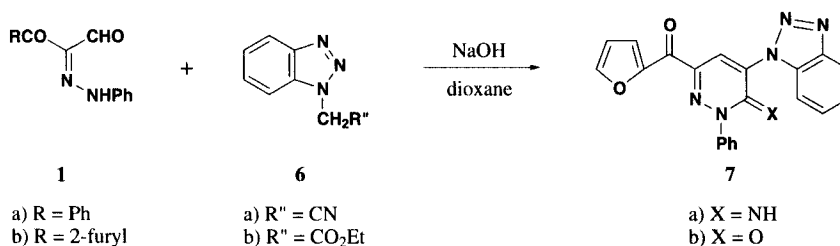


**Scheme 1**

2-Arylhyaazonopropanals (**1a,b**)<sup>11</sup> condensed readily with benzoylacetonitrile and cyanoacetamide to yield pyridazin-6-imines **3a-d**. Similar to formation of 5-benzoylamino-3-aro-ylpyridazi-

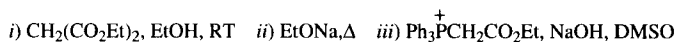
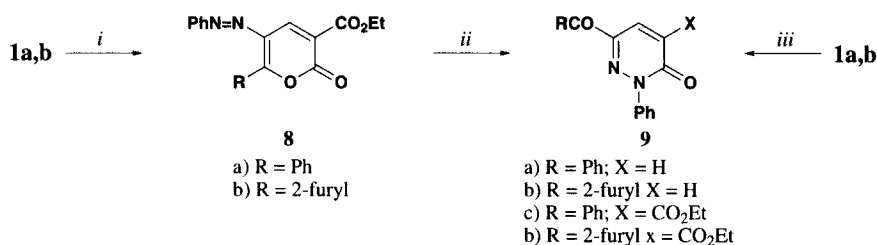
nones from hippuric acid in acetic anhydride,<sup>11</sup> **1a,b** readily reacted with glycine in refluxing acetic anhydride to yield 5-acetylaminopyridazin-6-ones **5a,b** in good yields (cf. Scheme 1). Structures **5** were preferred over **4** based on the fact that the reaction products are colorless and stable under conditions which would effect ring-opening of **4a,b**. For example, compound **5a** was recovered nearly unaffected after long reflux with aniline in acetic acid and sodium acetate, conditions which readily cause ring-opening of oxazolones.<sup>13</sup>

Arylhydrazone **1b** also condensed with benzotriazolylacetonitrile (**6a**) and ethyl benzotriazolylacetate (**6b**) to yield the benzotriazolylpyridazin-6-imine **7a** and pyridazin-6-one **7b** (cf. scheme 2). Although benzotriazolylacetonitriles are reported to have active methylene moiety,<sup>12</sup> to our knowledge this is the first reported condensation of such methylenes with aldehydes.



Scheme 2

Treatment of **1a,b** with diethyl malonate in ethanol at room temperature in the presence of diethylamine, resulted in good yields of the colored arylazopyran-2-ones **8a,b**; upon reflux in ethanolic sodium ethoxide, the latter compounds isomerized to **9a,b** which were previously obtained directly<sup>11</sup> from the reaction of **1a,b** with diethyl malonate in refluxing ethanol and in presence of piperidine. Compounds **1a,b** reacted readily with carbethoxymethyl triphenyl-phosphonium chloride in dimethyl sulfoxide in the presence of sodium hydride to yield pyridazin-6-ones **9c,d** (cf. Scheme 2); this is related to the reported reactivity of 2-arylhydrazonoketones toward Wittig reagents.<sup>14</sup>



Scheme 3

## EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Shimadzu IR-740 spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker AC-80 spectrometer with [D<sub>6</sub>] DMSO as solvent and TMS as internal standards; chemical shifts were reported in δ units (ppm).

Mass spectra were measured on GC/MS INCOS XL Finnigan MAT. Microelemental analysis were performed on LECO CHNS-932. Compounds **1a,b** were prepared following our recently published procedure.<sup>11</sup>

**Preparation of 1-Aryl-5-benzoyl-1,6-dihydro-6-imino-3-substituted Pyridazines (3). General Procedure.**- To a stirred solution of **1** (10 mmol) and benzoylacetonitrile (1.45g, 10 mmol) in ethanol (50 mL), was added a few drops of piperidine. The reaction mixture was heated under reflux for 1h after which it was cooled to room temperature. The precipitate which formed was collected and crystallized from ethanol (**3a,b**) or dioxane (**3c,d**).

**Preparation of 3-Substituted-5-acetamido-1,6-dihydro-1-arylpyridazin-6-one (5a,b). General Procedure.**- To a solution of glycine 0.75g (10 mmol) in acetic anhydride (50 mL), was added **1** (10 mmol). The mixture was heated under reflux for 1h, cooled to room temperature. The precipitate which formed, was collected and successively crystallized from dioxane.

**Preparation of 2-Furoyl-5-benzotriazol-1-yl-phenyl-1,6-dihydropyridazine-6-imines (7a,b). General Procedure.**- A solution of **6** (0.01 mol) in dioxane (30 mL) was treated with sodium hydride (0.02 mol) and then with **1b** (0.01 mol). The reaction mixture was refluxed for 0.5h then treated with ethanol to decompose excess sodium hydride. The resulting solution was evaporated under vacuum and the solid residue was triturated with water, collected and crystallized from ethanol.

**Preparation of Ethyl 2-Oxo-5-phenylazo-6-substituted-2H-pyran-3-carboxylate (8a,b). General Procedure.**- To a stirred solution of **1** (0.01 mol) in diethylamine (30 mL), was added diethyl malonate (1.60g, 0.01 mol). The suspension was stirred for 3h at room temperature. The crude product was collected, washed twice with methanol and purified by recrystallization from methanol.

**Preparation of 3-Substituted-1,6-dihydro-1-phenylpyridazin-6-ones (9c,d). General Procedure.**- Carbethoxytriphenylphosphonium chloride [obtained in quantitative yield by the reaction of **8** triphenylphosphine (2.62g; 0.01 mol) and ethyl chloroacetate (1.2g; 0.01 mol) in dry benzene (30 mL) for two days at room temperature] was added in portions over 15 min. to a cold stirred solution of methylsulfinyl carbanion [prepared by adding sodium hydride (0.48g; 56% dispersion) to dry DMSO (12.5 mL) and heating on a water bath for 90 min.]; stirring was continued for 1h. After the addition was completed, the reaction mixture was heated at 50° (bath temperature) and then compound **1** (0.01 mol) was added in one portion to the stirred reaction mixture and stirring was continued for 1h at 50°. The reaction mixture was left to cool at room temperature and poured into water. The oily product, isolated by decanting the aqueous phase, was separated and triturated with petroleum ether (bp. 40-60°). The resulting solid was collected and crystallized from dioxane.

**TABLE 1.** Yield, mps, and Elemental Analyses for Compounds **3a-d**, **5a,b**, **8a,b** and **9a,b**

Cmpd	Yield (%)	mp. (°C)	Elemental Analyses (Found)		
			C	H	N
<b>3a</b>	71	159-161	75.97 (76.05)	4.52 (4.59)	11.08 (10.97)
<b>3b</b>	68	191-192	71.53 (71.53)	4.09 (4.16)	11.38 (11.26)
<b>3c</b>	75	257-259	67.91 (67.88)	4.43 (4.66)	17.60 (17.62)
<b>3d</b>	74	274-276	62.33 (61.96)	3.92 (4.01)	18.18 (18.07)
<b>5a</b>	84	226-228	68.46 (68.28)	4.43 (4.63)	12.61 (12.47)
<b>5b</b>	80	262-264	63.16 (63.43)	4.05 (4.06)	13.00 (12.90)
<b>7a<sup>b</sup></b>	75	258	65.96 (65.66)	3.69 (3.94)	21.98 (21.77)
<b>7b<sup>b</sup></b>	70	>300	65.93 (65.79)	3.68 (3.42)	17.95 (18.27)
<b>8a<sup>c</sup></b>	84	138-140	68.94 (68.87)	4.63 (4.43)	8.05 (8.05)
<b>8b</b>	81	165-166	63.90 (63.95)	4.17 (4.22)	8.28 (8.64)
<b>9a</b>	60	149-151	73.90 (73.75)	4.38 (4.16)	10.14 (10.25)
<b>9b</b>	67	197-199	67.67 (67.43)	3.79 (3.90)	10.52 (10.12)

a) All compounds are yellow unless otherwise stated. b) Brown in color. c) MS (EI):m/z = 348 (M<sup>+</sup>)

**TABLE 2.** Spectral Data for Compounds **3a-d**, **5a,b**, **8a,b** and **9a,b**

Cmpd	IR (cm <sup>-1</sup> )	<sup>1</sup> H NMR (δ <sub>H</sub> )	<sup>13</sup> C NMR (δ <sub>C</sub> )
<b>3a</b>	3415 (NH), 1637 (CO)	7.45-8.03 (m, 17H, 15H <sub>arom</sub> + H <sub>4</sub> and NH)	
<b>3b</b>	3410 (NH), 1650-1630 (CO)	6.65-6.72 (m, 1H <sub>furyl H-4</sub> ), 7.49-8.04 (m, 14H, 10H <sub>arom</sub> + 2H <sub>furyl H-4&amp; H-5</sub> )	193.19 & 187.9 (CO), 152.45 & 140.02 (C <sub>3</sub> &C <sub>5</sub> ), 139.24 (C <sub>6</sub> ), 138.87, 136.05, 135.76, 133.79, 132.74, 130.62, 130.0, 129.81, 129.67, 128.83, 128.06, 126.89 (aromatic, C <sub>4</sub> and furyl carbons)

TABLE 2. Continued...

Cmpd	IR (cm <sup>-1</sup> )	<sup>1</sup> H NMR (δ <sub>H</sub> )	<sup>13</sup> C NMR (δ <sub>C</sub> )
<b>3c</b>	3245 br (NH & NH <sub>2</sub> ), 1670 (CO), 1640 (amide CO)	7.43-7.99 (m, 12H, 10H <sub>arom</sub> + NH <sub>2</sub> ), 8.17 (s, 1H, H <sub>4</sub> ), 9.60 (br, s, NH)	
<b>3d</b>	3255, 3125 (NH & NH <sub>2</sub> ), 1684 (C), 1638 (amide CO)	6.64-6.70 (m, 1H <sub>furyl H-4</sub> ), 7.41-8.12 (m, 10H, 5H <sub>arom</sub> + 2H <sub>furyl H-4&amp; H-5</sub> + H <sub>4</sub> + NH <sub>2</sub> ), 10.27 (br, s, 1H, NH)	
<b>5a</b>	3270 (NH), 1693 & 1633 (CO)	2.26 (s, 3H, CH <sub>3</sub> ), 7.38-8.07 (m, 10H <sub>arom</sub> ), 8.66 (s, 1H, H <sub>4</sub> ), 10.04 (br, s, 1H, NH)	185.99 (CO), 170.99 (ring CO), 154.97 (amide CO), 143.62 (C <sub>3</sub> ), 141.28 (C <sub>5</sub> ), 136.91, 135.45, 132.86, 130.27, 128.57, 128.33, 127.97, 125.52 (aromatic C), 110.03 (C <sub>4</sub> ) & 24.10 (CH <sub>3</sub> )
<b>5b</b>	3425 (NH), 1632 (CO)	2.25 (s, 3H, CH <sub>3</sub> ), 6.66-6.73 (m, 1H <sub>furyl H-4</sub> ), 7.46-7.71 (m, 6H, 5H <sub>arom</sub> + 2H <sub>furyl H-3</sub> ), 8.60 (s, 1H, H <sub>4</sub> ), 9.90 (br, s, 1H, NH)	
<b>7a</b>	3449 (NH), 1646 (CO)		7.68-6.74 (m, 1H <sub>furyl H-4</sub> ), 7.50-8.06 (m, 13H, 2H <sub>furyl H-3&amp; H-5</sub> + 9H <sub>arom</sub> + H <sub>4</sub> + NH)
<b>7b</b>	1676 (ring CO), 1646 (acyl CO)	7.3-8.3 (m, aromatic H's)	
<b>8a</b>	1730 (ester CO), 1664 (ring CO)	1.35 (t, 3H, <i>J</i> = 8 Hz, CH <sub>3</sub> ), 4.49 (q, 2H, <i>J</i> = 8 Hz, OCH <sub>2</sub> ), 7.48-8.97 (m, 10H <sub>arom</sub> ), 8.30 (s, 1H, H <sub>4</sub> )	14.71 (CH <sub>3</sub> ), 60.85 (CH <sub>2</sub> ), 106.12 (C <sub>5</sub> ), 119.64 (C <sub>3</sub> ), 142.9 (C <sub>4</sub> ), 151.18 (C <sub>6</sub> ), 161.63 (ring CO), 193.15 (CO), 143.25-125.83 (aromatic C)
<b>8b</b>	1739 (ester CO), 1670 (ring CO)	1.30 (t, 3H, <i>J</i> = 8 Hz, CH <sub>3</sub> ), 4.37 (q, 2H, <i>J</i> = 8 Hz, OCH <sub>2</sub> ), 6.67-6.76 (m, 1H <sub>furyl H-4</sub> ), 7.76-7.74 (m, 5H, aromatic & 1H <sub>furyl H-3</sub> ), 8.29 (s, 1H, pyrane H <sub>4</sub> )	

TABLE 2. Continued...

Cmpd	IR (cm <sup>-1</sup> )	<sup>1</sup> H NMR (δ <sub>H</sub> )	<sup>13</sup> C NMR (δ <sub>C</sub> )
<b>9a</b>	1670 & 1634 (CO)	7.27 (d, 1H, H <sub>5</sub> , <i>J</i> = 8.6 Hz), 7.35-8.07 (m, 11H <sub>arom.H</sub> and H <sub>4</sub> )	
<b>9b</b>	1670 & 1634 (CO)	6.46-6.56 (m, 1H <sub>furyl H-4</sub> ), 7.09 (d, 1H, H <sub>5</sub> , <i>J</i> = 9Hz)	7.24-7.70 (m, 7H, 5H <sub>arom</sub> + 2H <sub>furyl H-3&amp; H3</sub> )

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