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A novel approach to the titled ring system starting from conveniently available chalcones **1** is proposed. It involves a catalysed exchange of hydrogen cyanide between acetone cyanohydrin and **1**. The resulting  $\gamma$ -keto-nitriles **2** give the expected 4,6-diarylpyridazinones **4** and **5** *via* hydrolysis and cyclisation by hydrazine. The action of phosphorus oxychloride on **5** followed by that of amines provides aminopyridazines **7**.

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Arylpyridazinones have been a subject of intensive synthetic investigations, because they possess a wide spectrum of pharmacological potencies. Nannini [1] reported that 5,6-diphenylpyridazinones exhibited analgesic and anti-inflammatory activities. Recently, 6-aryl-4,5-dihydropyridazinones have been of interest as a new class of compounds with positive inotropic activity [2,3,4,5] but also as hypotensive agents [6,7] and platelet aggregation inhibitors [8,9].

A search of the literature showed that preparation of 4,6-diaryl-4,5-dihydropyridazinones was performed starting from  $\beta$ -(4-chloro-3-methylbenzoyl)-acrylic acid [10,11]. We report in this paper a new approach to the synthesis of this pyridazine ring system from chalcones **1**. Unlike the previous procedure [11], introduction of different substituents on the phenyl ring in 6-position of pyridazinone is possible.

In the initial step of the synthesis, addition of hydrogen cyanide to substituted chalcones is performed by an exchange with acetone cyanohydrin according to the procedure described by Betts and Davey [12]. The  $\gamma$ -keto-nitriles **2** are hydrolysed by 10 *N* hydrochloric acid to the corresponding 2,4-diaryl-4-oxobutanoic acids **3**. Condensation with hydrazine hydrate in refluxing 1-butanol smoothly

converts **3** into the expected 4,6-diaryl-4,5-dihydro-3(2*H*)-pyridazinones **4a-d**, while a similar reaction with methylhydrazine leads to **4e-g** (Scheme I). Then, dihydropyridazinones **4** are dehydrogenated by bromination and dehydrobromination in acetic acid to give 4,6-diaryl-3-pyridazinones **5a-e**. Treated with phosphorus oxychloride, **5a-c** give 3-chloropyridazines **6a-c**. In the final step of the reaction scheme, compounds **6a-c** react with amines to afford 3-aminopyridazines **7a-h**.

The structure of compounds **4**, **5**, **6** and **7** was established from their analytical and spectral data (Tables 1 and 2).

Most prepared pyridazinones could present an analgesic and/or an anti-inflammatory profile. On the other hand, biological activity of compounds **7a** and **7b** is similar to 3-dimethylamino-5-(2',6'-dichlorobenzylidene)-6-methyl-(4*H*)-pyridazine [13]: they enhance prostacyclin biosynthesis and decrease thromboxane formation *in vitro*.

## EXPERIMENTAL

All melting points were determined on a Kofler apparatus and were uncorrected. The infrared spectra were recorded on a Beckman 4240 spectrophotometer. The proton nmr spectra were recorded on a Varian EM 360 A in DMSO *d*<sub>6</sub>.

Scheme I

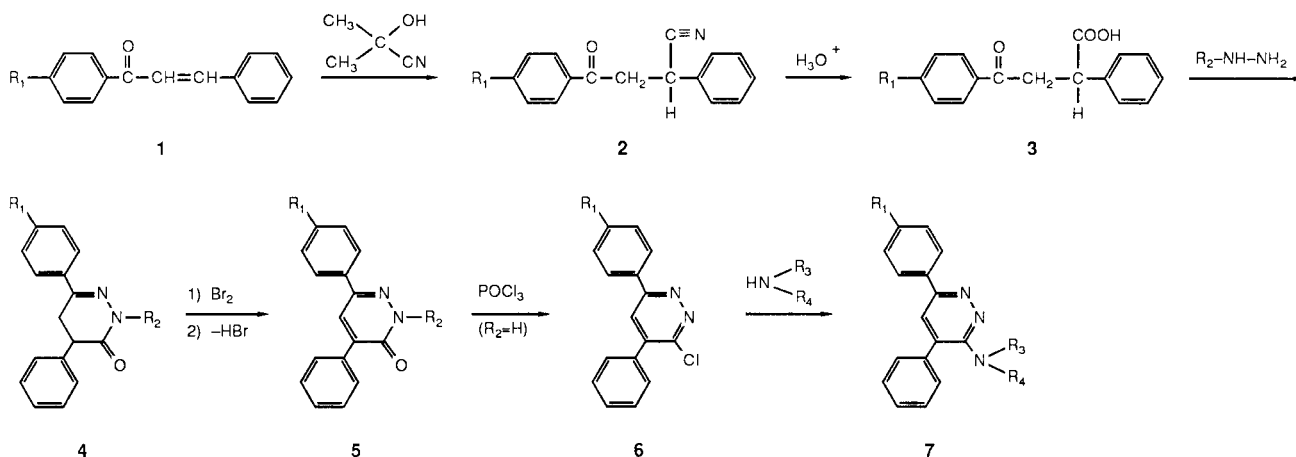


Table 1  
Physical and Analytical Data for Compounds 4, 5, 6 and 7





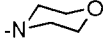
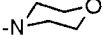
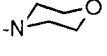
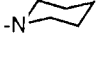


Compound No.	R <sub>1</sub>	R <sub>2</sub>	Functional group on 3-C	Yield [a] %	$\alpha_D^{20}$	Molecular Formula (M W)	C	H	N	O	Hal	
4a	H	H	=O	69	163	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O (250)	76.80 76.63	5.60 5.62	11.20 10.99	6.40 6.69		
4b	F	H	=O	75	164	C <sub>16</sub> H <sub>13</sub> FN <sub>2</sub> O (268)	71.64 71.78	4.85 4.75	10.45 10.27	5.97 6.20	7.09 7.00	
4c	Cl	H	=O	40	165	C <sub>16</sub> H <sub>13</sub> ClN <sub>2</sub> O (284.5)	67.49 67.22	4.57 4.60	9.84 9.54	5.62 5.84	12.48 13.37	
4d		H	=O	51	220	C <sub>19</sub> H <sub>16</sub> N <sub>4</sub> O (316)	72.15 72.23	5.06 5.10	17.73 17.31	5.06 5.65		
4e	H	CH <sub>3</sub>	=O	45	105	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O (264)	77.27 77.03	6.06 6.13	10.61 10.69	6.06 6.06		
4f	F	CH <sub>3</sub>	=O	90	150	C <sub>17</sub> H <sub>15</sub> FN <sub>2</sub> O (282)	72.34 71.93	5.32 5.41	9.93 9.89	5.67 6.21	6.74 6.54	
4g	Cl	CH <sub>3</sub>	=O	84	146	C <sub>17</sub> H <sub>15</sub> ClN <sub>2</sub> O (298.5)	68.34 68.09	5.03 5.08	9.38 9.31	5.36 5.80	11.89 11.87	
5a	H	H	=O	93	184	C <sub>16</sub> H <sub>12</sub> N <sub>2</sub> O (248)	77.42 77.02	4.84 4.80	11.29 11.51	6.45 6.70		
5b	F	H	=O	98	210	C <sub>16</sub> H <sub>11</sub> FN <sub>2</sub> O (266)	72.18 72.48	4.14 4.17	10.53 10.48	6.01 6.10		
5c	Cl	H	=O	96	224	C <sub>16</sub> H <sub>11</sub> ClN <sub>2</sub> O (282.5)	67.97 67.87	3.89 3.94	9.91 9.57	5.66 6.05	7.14 6.77	
5d		H	=O	94	205	C <sub>19</sub> H <sub>14</sub> N <sub>4</sub> O (314)	72.61 72.43	4.46 4.34	17.83 17.71	5.10 5.25	12.57 12.57	
5e	H	CH <sub>3</sub>	=O	93	120	C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O (262)	77.86 77.91	5.34 5.26	10.69 10.55	6.11 6.28		
6a	H	-	-Cl	99	100	C <sub>16</sub> H <sub>11</sub> ClN <sub>2</sub> (266.5)	72.04 71.97	4.13 4.13	10.51 10.10		13.32 13.94	
6b	F	-	-Cl	97	152	C <sub>16</sub> H <sub>10</sub> ClFN <sub>2</sub> (284.5)	67.49 67.54	3.51 3.29	9.84 9.86		12.48 12.31 6.68 6.72	} Cl } F
6c	Cl	-	-Cl	80	175	C <sub>16</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> (301)	63.79 63.85	3.32 3.37	9.30 9.15		23.59 23.63	
7a	H	-		96	108	C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> (275)	78.55 78.29	6.18 6.18	15.27 15.33			
7b	Cl	-		97	136	C <sub>18</sub> H <sub>16</sub> ClN <sub>3</sub> (309.5)	69.79 69.86	5.17 5.38	13.57 13.23		11.47 11.53	
7c	H	-		98	136	C <sub>20</sub> H <sub>19</sub> N <sub>3</sub> O (317)	75.71 75.70	5.99 5.97	13.25 13.20	5.05 5.03		
7d	F	-		98	120	C <sub>20</sub> H <sub>18</sub> FN <sub>3</sub> O (335)	71.64 71.20	5.38 5.44	12.53 12.12	4.78 5.58	5.67 5.49	
7e	Cl	-		85	154	C <sub>20</sub> H <sub>18</sub> ClN <sub>3</sub> O (351.5)	68.28 68.07	5.12 5.18	11.95 11.98	4.55 4.62	10.10 10.21	
7f	H	-		65	139	C <sub>21</sub> H <sub>21</sub> N <sub>3</sub> (315)	80.00 79.52	6.67 6.81	13.33 13.30			

Table 1 Continued

Compound No.	R <sub>1</sub>	R <sub>2</sub>	Functional group on 3-C	Yield [a] %	ap °C	Molecular Formula (MW)	C	H	N	O	Hal
7g	F	-		63	130	C <sub>21</sub> H <sub>20</sub> FN <sub>3</sub> (333)	75.68 75.47	6.01 6.12	12.61 12.83		5.70 5.58
7h	Cl	-		98	131	C <sub>21</sub> H <sub>20</sub> ClN <sub>3</sub> (349.5)	72.10 71.91	5.72 5.58	12.02 12.12		10.16 10.48

[a] Crude Products.

Table 2

Spectral Data for Compounds 4, 5, 6 and 7

Compound No.	ν NH	ν C=O	IR (Potassium bromide) cm <sup>-1</sup>				1H NMR (DMSO-d <sub>6</sub> ) δ [ppm]
			ν C=N	ν C=C			
4a	3240	1670	1600	—	1490	1440	3.3 (m, 2H, CH <sub>2</sub> ), 3.9 (m, 1H, CH), 7.6 (m, 10H, Ar), 11.4 (s, 1H, NH)
4b	3220	1680	1610	—	1510	1450	3.4 (m, 2H, CH <sub>2</sub> ), 3.9 (m, 1H, CH), 7.5 (m, 9H, Ar), 11.5 (s, 1H, NH)
4c	3250	1670	1610	—	1495	1450	3.3 (m, 2H, CH <sub>2</sub> ), 3.9 (m, 1H, CH), 7.6 (m, 9H, Ar), 11.2 (s, 1H, NH)
4d	3240	1660	1610	—	1520	1450	3.4 (m, 2H, CH <sub>2</sub> ), 3.9 (m, 1H, CH), 6.6 (m, 1H, =CH), 8.0 (m, 11H, Ar, 2=CH), 11.4 (s, 1H, NH)
4e	—	1650	1600	—	1500	1450	3.3 (m, 2H, CH <sub>2</sub> ), 3.4 (s, 3H, CH <sub>3</sub> ), 3.9 (m, 1H, CH), 7.5 (m, 9H, Ar)
4f	—	1660	1610	—	1510	1460	3.3 (m, 2H, CH <sub>2</sub> ), 3.4 (s, 3H, CH <sub>3</sub> ), 4.0 (m, 1H, CH), 7.6 (m, 9H, Ar)
4g	—	1655	1600	—	1500	1455	3.3 (m, 2H, CH <sub>2</sub> ), 3.4 (s, 3H, CH <sub>3</sub> ), 4.0 (m, 1H, CH), 7.6 (m, 9H, Ar)
5a	3250	1650	1590	—	1490	1450	7.8 (m, 11H, Ar, =CH), 13.4 (s, 1H, NH)
5b	3240	1680	1600	—	1510	1490	7.7 (m, 10H, Ar, =CH), 13.4 (s, 1H, NH)
5c	3230	1660	1600	—	1500	1450	7.8 (m, 10H, Ar, =CH), 13.4 (s, 1H, NH)
5d	3240	1660	1600	—	1520	1450	6.6 (s, 1H, =CH), 8.0 (m, 12H, Ar, 2=CH), 13.4 (s, 1H, NH)
5e	—	1645	1595	—	1490	1450	3.9 (s, 3H, CH <sub>3</sub> ), 7.8 (m, 11H, Ar, =CH)
6a	—	—	1600	1570	1490	1440	7.9 (m, 11H, Ar, =CH)
6b	—	—	1600	1580	1490	1450	7.9 (m, 10H, Ar, =CH)
6c	—	—	1600	1580	1490	1445	8.0 (m, 10H, Ar, =CH)
7a	—	—	1580	1520	1480	1450	2.8 (s, 6H, 2CH <sub>3</sub> ), 7.9 (m, 11H, Ar, =CH)
7b	—	—	1590	1530	1490	1450	2.7 (s, 6H, 2CH <sub>3</sub> ), 7.8 (m, 10H, Ar, =CH)
7c	—	—	1600	1510	1490	1450	3.2 (m, 4H, 2CH <sub>2</sub> N), 3.6 (m, 4H, 2CH <sub>2</sub> O), 7.9 (m, 11H, Ar, =CH)
7d	—	—	1600	1510	1500	1450	3.2 (m, 4H, 2CH <sub>2</sub> N), 3.6 (m, 4H, 2CH <sub>2</sub> O), 7.9 (m, 10H, Ar, =CH)
7e	—	—	1600	1500	1490	1450	3.2 (m, 4H, 2CH <sub>2</sub> N), 3.7 (m, 4H, 2CH <sub>2</sub> O), 8.0 (m, 10H, Ar, =CH)
7f	—	—	1580	1510	1490	1450	1.6 (m, 6H, 3CH <sub>2</sub> ), 3.2 (m, 4H, 2CH <sub>2</sub> N), 7.9 (m, 11H, Ar, =CH)
7g	—	—	1600	1510	1490	1440	1.5 (m, 6H, 3CH <sub>2</sub> ), 3.1 (m, 4H, 2CH <sub>2</sub> N), 7.8 (m, 10H, Ar, =CH)
7h	—	—	1590	1510	1490	1430	1.5 (m, 6H, 3CH <sub>2</sub> ), 3.2 (m, 4H, 2CH <sub>2</sub> N), 7.9 (m, 10H, Ar, =CH)

Resonance positions are given on the  $\delta$  scale (parts per million) relative to internal tetramethylsilane. The nmr peaks were designated as follows: s, singlet; m, multiplet.

Elemental analysis were performed at the Service Central d'Analyses, Centre National de la Recherche Scientifique, 69390 Vernaison, France.

Chalcones **1** were prepared from substituted acetophenones using the method of Kohler [14].

4-Acetylphenylpyrazole was synthesized using the method of Khan [15].

#### 2,4-Diaryl-4-oxobutanoic Acids **3a-d**.

The 2,4-diaryl-4-oxonitriles **2a-d** (0.01 mole) in 10 N hydrochloric acid (50 ml) were stirred at room temperature for 2 hours, then refluxed on a steambath for 3 hours. The reaction mixture was cooled and the precipitate formed was collected by filtration, washed with water and dried.

In the case of compound **3d**, after refluxing, the solution was evaporated *in vacuo*. The residue was triturated with water to provide the expected acid.

#### 4,6-Diaryl-4,5-dihydro-3(2H)-pyridazinones **4a-g**.

A mixture of 0.01 mole of acid **3** and 0.01 mole of hydrazine hydrate or methylhydrazine in 1-butanol (50 ml) was refluxed for 6 hours. Then the mixture was cooled and the crude product which separated was filtered off and recrystallized from ethanol.

#### 4,6-Diaryl-3-pyridazinones **5a-e**.

A vigorously stirred solution of 0.01 mole of compound **4** in glacial acetic acid (50 ml) was heated to 70° and then treated portionwise with bromine (0.01 mole) for 15 minutes. The mixture was stirred further for 3 hours and poured into ice water. The solid which separated was filtered off and recrystallized from ethanol to give **5**.

#### 4,6-Diaryl-3-chloropyridazines **6a-c**.

A suspension of 0.01 mole of pyridazinone **5** in phosphorus oxychloride (25 ml) was heated to 90° for 2 hours. The reaction mixture was poured gradually into crushed ice and the solid that separated was filtered and dried.

#### 4,6-Diaryl-3-dimethylaminopyridazines **7a-b**.

A solution of 0.005 mole of 3-chloropyridazine **6a** or **6c** in dimethyl-

amine (20 ml) was heated in a bomb apparatus at 160° for 6 hours. After cooling, the solution was evaporated to dryness *in vacuo*. The solid residue was triturated with water, until crystallization. Compounds **7a-b** were recrystallized from ethanol-water mixture (60:40).

#### 4,6-Diaryl-3-azacycloalkylpyridazines **7c-h**.

A solution of 0.01 mole of a 3-chloropyridazine **6** in morpholine or piperidine (30 ml) was refluxed for 7 hours. After evaporation *in vacuo*, the residue was triturated with diisopropyl ether and washed with water to provide the expected aminopyridazines **7c-h**.

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