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*N*-1-Unsubstituted-3-aryl-4-pyrazoleacetic acids and their 4,5-dihydro derivatives can conveniently be prepared by cyclization of 3-benzoyl-3-butenic acids with hydrazine hydrate in acetic acid and subsequent treatment with bromine in acetic acid or, respectively, with diluted mineral acids.

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The class of pyrazole-4-acetic acids is mainly represented in medicinal chemistry by 1,3-diaryl derivatives exhibiting antiinflammatory and analgesic activity [1,2].

Having planned research on the properties of 3-aryl-4-

pyrazoleacetic acids and of their 4,5-dihydro derivatives with non aromatic substituents at the *N*-1 position, the unsubstituted acids **1** and **2** were needed as intermediates. A survey of the literature unexpectedly revealed that classes **1** and **2** were unknown, the only compounds related

Scheme 1

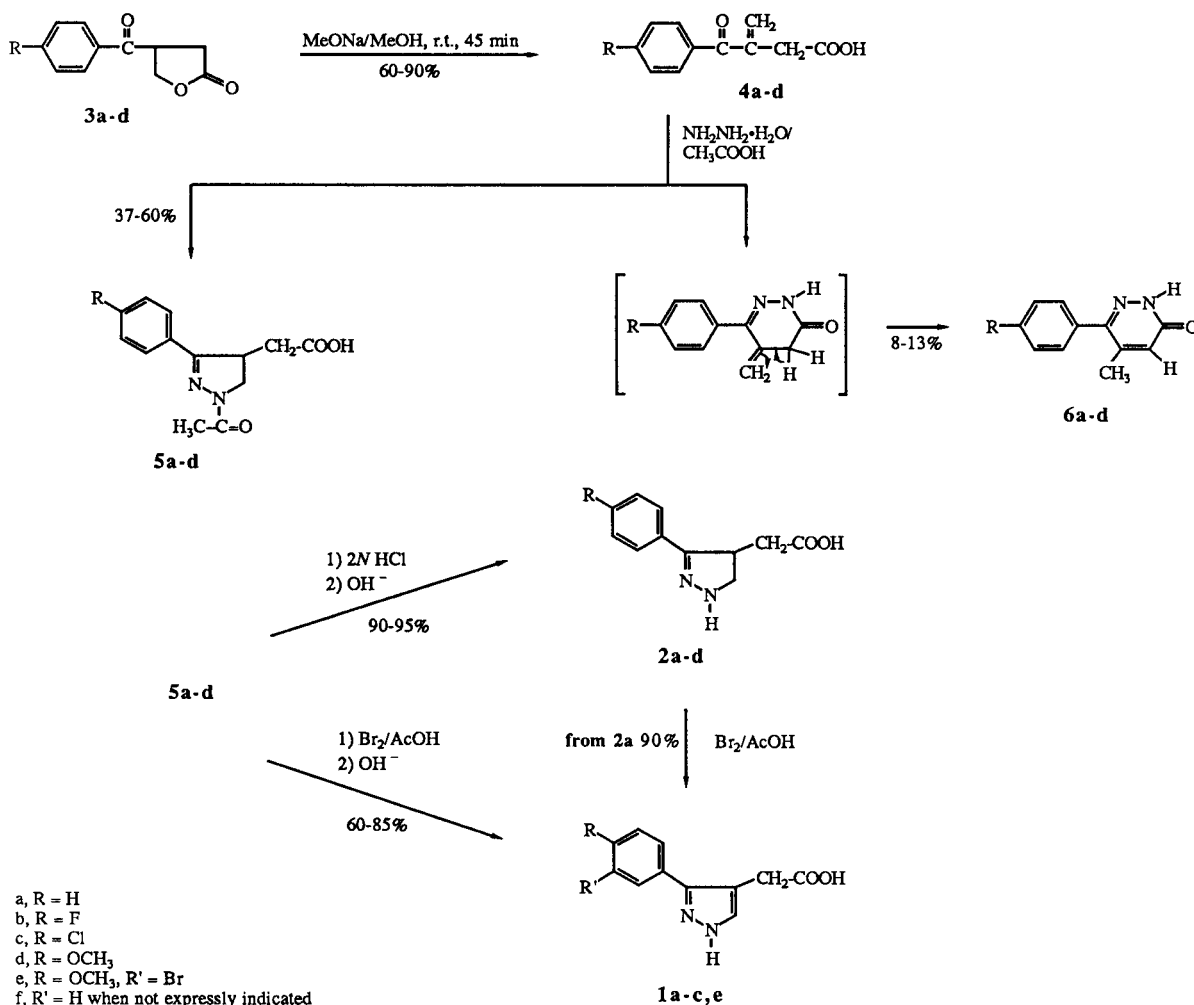


Table 1  
Physical Properties and Spectral Data of Compounds 1,2,4,5 and 6 prepared

Compound	R	Yield %	mp (°C) [a] (solvent)	Molecular Formula or Lit (°C)	<sup>1</sup> H-NMR (DMSO/TMS) d, J (Hz)
4a	H	60	63-65	60-65 [8]	3.5 (s, 2H, -CH <sub>2</sub> -), 5.77- 5.98 (2 app s, 2H, =CH <sub>2</sub> ), 7.1-8.1 (m, 5H arom), 9.25 (br, s, 1H)
4b	F	87	104-108 (ethanol)	C <sub>11</sub> H <sub>9</sub> FO <sub>3</sub> (208.1)	3.5 (s, 2H, -CH <sub>2</sub> -), 5.7, 5.95 (2 app s, 2H, =CH <sub>2</sub> ), 6.9-7.9 (m, 4H arom), 9.25 (br, s, 1H)
4c	Cl	91	88-90 (ethanol)	C <sub>11</sub> H <sub>9</sub> ClO <sub>3</sub> (224.5)	3.5 (s, 2H, -CH <sub>2</sub> -), 5.8, 6.1 (2 app s, 2H, =CH <sub>2</sub> ), 7.5-7.8 (dd, 4H arom), 9.5 (br, s, 1H)
4d	OCH <sub>3</sub>	90	116-119 (ethanol)	C <sub>12</sub> H <sub>12</sub> O <sub>4</sub> (220.1)	3.5 (s, 2H, -CH <sub>2</sub> -), 3.8(s, 3H, OCH <sub>3</sub> ), 5.69, 5.89 (2 app s, 2H, =CH <sub>2</sub> ), 6.83-7.75 (dd, 4H arom), 9.4 (br, s, 1H)
5a	H	60	207-210 (ethanol)	C <sub>13</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> (264.3)	2.1 (s, 3H, CH <sub>3</sub> ), 2.3 (m, 2H, CH <sub>2</sub> COOH), 3.6-3.9 (m, 3H, CHCH <sub>2</sub> ), 7.1-7.5 (m, 5H arom)
5b	F	45	199-202 (ethanol)	C <sub>13</sub> H <sub>13</sub> FN <sub>2</sub> O <sub>3</sub> (264.3)	2.2 (s, 3H, CH <sub>3</sub> ), 2.6 (m, 2H, CH <sub>2</sub> COOH), 3.9-4.1 (m, 3H, CHCH <sub>2</sub> ), 7.0-7.9 (m, 4H arom)
5c	Cl	41	180-182 (ethanol)	C <sub>13</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>3</sub> (280.2)	2.2 (s, 3H, CH <sub>3</sub> ), 2.6 (m, 2H, CH <sub>2</sub> COOH), 3.9-4.1 (m, 3H, CHCH <sub>2</sub> ), 7.0-7.9 (m, 4H arom)
5d	OCH <sub>3</sub>	37	190-192 (ethanol)	C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub> (276.2)	2.2 (s, 3H, CH <sub>3</sub> ), 2.6 (m, 2H, CH <sub>2</sub> COCH), 3.8 (s, 3H, OCH <sub>3</sub> ), 3.9-4.1 (m, 3H, CHCH <sub>2</sub> ), 6.8-7.6 (dd, 4H arom)
6a	H	10	210-212 (ethanol)	218-219 [6]	2.2 (s, 3H, CH <sub>3</sub> ), 7.0 (s, 1H, H-4), 7.5 (s, 5H arom)
6b	F	13	244-245 (ethanol)	243-245 [9]	2.1 (s, 3H, CH <sub>3</sub> ), 6.9 (s, 1H, H-4), 7.2-7.7 (m, 4H arom)
6c	Cl	8	220-222 (ethanol)	224-225 [10]	2.1 (s, 3H, CH <sub>3</sub> ), 7.0 (s, 1H, H-4), 7.3-7.7 (s, 4H arom)
6d	OCH <sub>3</sub>	10	202-203 (ethanol)	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> (216.2)	2.2 (s, 3H, CH <sub>3</sub> ), 4.0 (s, 3H, OCH <sub>3</sub> ), 7.0 (s, 1H, H-4), 7.2-7.6 (dd, 4H arom)
1a	H	78 [b], 90 [c]	220-225 [d] (ethanol-ether)	C <sub>11</sub> H <sub>11</sub> BrN <sub>2</sub> O <sub>2</sub> (283.1)	3.6 (s, 2H, CH <sub>2</sub> COOH), 7.3-7.6 (m, 6H, C <sub>6</sub> H <sub>5</sub> + H-5)
1b	F	60 [e]	215 dec (ethanol-ether)	C <sub>11</sub> H <sub>10</sub> BrFN <sub>2</sub> O <sub>2</sub> (301.1)	3.55 (s, 2H, CH <sub>2</sub> COOH), 6.95-7.85 (m, 5H, C <sub>6</sub> H <sub>4</sub> + H-5)
1c	Cl	85 [e]	150 (ethanol-ether)	C <sub>11</sub> H <sub>10</sub> BrClN <sub>2</sub> O <sub>2</sub> (317.1)	3.50 (s, 2H, CH <sub>2</sub> COOH), 6.90-7.80 (m, 5H, C <sub>6</sub> H <sub>4</sub> + H-5)
1e	2-Br, 4-OCH <sub>3</sub>	70 [e]	170 dec (ethanol-ether)	C <sub>12</sub> H <sub>12</sub> Br <sub>2</sub> N <sub>2</sub> O <sub>3</sub> (392.1)	3.58 (s, 2H, CH <sub>2</sub> COOH), 3.8 (s, 3H, OCH <sub>3</sub> ), 6.85-7.75 (m, 4H, C <sub>6</sub> H <sub>3</sub> + H-5)
2a	H	90	152-154 [f] (ethanol-ether)	C <sub>11</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub> (240.7)	2.9 (d, 2H, J = 6, CH <sub>2</sub> COOH), 3.65-4.65 (m, 3H, CHCH <sub>2</sub> ), 7.35-7.85 (m, 5H arom)
2b	F	95	177-180 (ethanol-ether)	C <sub>11</sub> H <sub>12</sub> ClFN <sub>2</sub> O <sub>2</sub> (258.6)	2.85 (d, 2H, J = 6, CH <sub>2</sub> COOH), 3.6-4.2 (m, 3H, CHCH <sub>2</sub> ), 7.0-7.9 (m, 4H arom)
2c	Cl	90	154-158 (ethanol-ether)	C <sub>11</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub> (274.6)	2.85 (d, 2H, J = 6, CH <sub>2</sub> COOH), 3.6-4.2 (m, 3H, CHCH <sub>2</sub> ), 7.1-7.9 (m, 4H arom)
2d	OCH <sub>3</sub>	91	200-203 (ethanol-ether)	C <sub>12</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>2</sub> (270.7)	2.9 (d, 2H, J = 6, CH <sub>2</sub> COOH), 3.75-4.3 (m, 6H, OCH <sub>3</sub> + CHCH <sub>2</sub> ), 7.02-7.72 (dd, 4H arom)

[a] For compounds 1 and 2 melting points refer to the salts. [b] From 5a. [c] From 2a. [d] Melting point of the free base 132-135°. [e] From the corresponding 5. [f] Melting point of the free base 92-95°.

Table 2  
Elemental Analyses

Compound	MW	C	H	Br	Cl	F	N	%
<b>5a</b>	246.3	63.36	5.68				11.37	Calcd. Found
		63.12	5.34				11.12	
<b>5b</b>	264.2	59.04	4.92			7.19	10.59	
		58.98	4.86			7.05	10.11	
<b>5c</b>	280.2	55.67	4.64		12.49		9.99	
		55.91	4.98		12.25		10.15	
<b>5d</b>	276.2	60.85	5.84				10.14	
		60.85	5.94				10.21	
<b>2a</b>	240.7	54.90	5.44		14.71		11.63	
		54.61	5.40		14.73		11.35	
<b>2b</b>	258.6	51.18	4.65		13.69	7.36	10.85	
		50.97	4.75		13.35	7.06	10.76	
<b>2c</b>	274.6	48.06	4.37		25.49		10.19	
		47.96	4.21		25.23		10.05	
<b>2d</b>	270.7	53.24	5.58		13.09		10.34	
		53.41	5.87		13.21		10.01	
<b>1a</b>	283.1	46.66	3.91	28.25			9.89	
		46.59	3.73	28.00			9.75	
<b>1b</b>	301.1	43.84	3.32	26.56		6.31	9.29	
		43.77	3.23	26.65		6.13	9.35	
<b>1c</b>	317.1	41.63	3.15	25.22	11.03		8.83	
		41.92	3.01	24.95	10.97		8.65	
<b>1e</b>	392.1	36.72	3.06	40.80			7.14	
		36.60	3.21	40.75			7.03	

to them were substituted by aryl groups at N-1 and/or by alkyl or aryl groups at C-5 [1-4].

We report in this paper a synthesis of **1** and **2** of general utility, starting from the readily available  $\beta$ -aroyl- $\gamma$ -butyrolactones **3**. Reaction of **3** with equimolar methanolic sodium methoxide gave 3-aroyl-3-butenic acids **4**, which appeared suitable to add hydrazine to the 1,3-conjugated double bonds, by analogy with the previously reported synthesis of 3-aryl-4-methyl-4,5-dihydropyrazoles from 1-aryl-2-methyl-2-propen-1-ones [5]. A first attempt to condense representative **4a** and hydrazine hydrate in refluxing ethanol was unsuccessful, a complex mixture of unidentified products being isolated. However, by using acetic acid as the solvent we obtained in a ratio 6:1 two compounds analysed for  $C_{13}H_{14}N_2O_3$  (**5a**) and  $C_{11}H_{10}N_2O$  (**6a**) which could easily be separated because of the solubility of **5a** in aqueous sodium bicarbonate.

While **6a** was found to be the known 6-phenyl-5-methyl-3(2*H*)-pyridazinone [6], the main product **5a** (60%) was identified by spectral properties (ir,  $^1H$  nmr) as 1-acetyl-3-

phenyl-4,5-dihydro-4-pyrazoleacetic acid. Chemical evidence of this structure came from the conversion of **5a** in refluxing 2*N* hydrochloric acid to a compound  $C_{11}H_{12}N_2O_2$  **2a** (isolated as the hydrochloride) to which the structure, 3-phenyl-4,5-dihydro-4-pyrazoleacetic acid was assigned on the basis of spectral data and of its reconversion into the starting **5a** with acetic anhydride in ether. As expected, bromine addition to **2a** in acetic acid solution followed by dehydrobromination, gave 3-phenyl-4-pyrazoleacetic acid **1a** in 90% yield.

We have found, however, that a more convenient procedure to **1a** could be performed, simply by treating **5a** with bromine in refluxing acetic acid. This conversion could be interpreted involving bromination-dehydrobromination of **5a** to give 1-acetyl-3-phenyl-4-pyrazoleacetic acid as the intermediate, followed by cleavage of the labile  $N_1$ -acetyl group [7] by the action of hydrogen bromide. Addition of water to the starting mixture did not improve the yield of **1a**.

The extension of the above described procedure to bu-

tenoic acids **4b-d** provided a convenient approach to **2b-d** and **1b,c,e**. It is to be noted that in the case of the aromatization of **5d** ( $R = OCH_3$ ) a concomitant bromination of the activated aromatic ring occurred, giving rise to the 3-bromo-4-methoxyphenyl derivative **1e**.

### EXPERIMENTAL

Melting points were determined with a Büchi 510 capillary melting point apparatus and are uncorrected. All elemental analyses (C,H,Br,Cl,F,N) of the new substances were within  $\pm 0.4$  of the theoretical values. The  $^1H$  nmr spectra were recorded on a Hitachi Perkin-Elmer R 600 FT spectrometer with tetramethylsilane as the internal standard.

#### 3-Benzoyl-3-butenic Acids **4a-d**.

Compounds were prepared from the appropriate  $\beta$ -benzoyl- $\gamma$ -butyrolactone (1 mole) and 1% methanolic sodium methoxide (1 mole) which were allowed to react at room temperature for 15 minutes according to a previously reported method [8] (see Table 1).

#### *N*-1-Acetyl-3-(*p*-substituted-phenyl)-4,5-dihydro-4-pyrazoleacetic Acids **5a-d** and 6-(*p*-Substituted-phenyl)-5-methyl-3(2*H*)-pyridazinones **6a-d**.

A mixture of the required 3-(*p*-substituted-benzoyl)-3-butenic acid (**4**, 1 mole) and hydrazine hydrate (2 moles) was refluxed in acetic acid (1/5 w/v) for 3 hours. After evaporation of the acetic acid the mixture was poured onto ice, extracted with chloroform and dried. The solvent was then evaporated and the residue treated with a 5% sodium bicarbonate solution. The insoluble material, mainly formed by the pyridazinone **6**, was filtered off while the filtrate was acidified with 6*N* hydrochloric acid to give the desired *N*-1-acetyl-3-substituted-phenyl-4,5-dihydro-4-pyrazoleacetic acid, which was crystallized from a suitable solvent. The pyridazinone **6** was in turn purified by silica gel chromatography, eluting with chloroform/methanol 9/1 (see Table 1).

#### 3-(*p*-Substituted-phenyl)-4,5-dihydro-(1*H*)-4-pyrazoleacetic Acids **2a-d**.

A suspension of the required **5** in 2*N* hydrochloric acid (ratio 1/15 w/v) was refluxed for 2 hours. The resulting solution was

evaporated to dryness to give crude **2** as the hydrochloride which was crystallized from ethanol-ether (see Table 1).

In the case of **2a** the free base was obtained by adjusting an aqueous solution of the salt to pH 4.

#### 3-(*p*-Substituted-phenyl)-(1*H*)-4-pyrazoleacetic Acids **1a-d**.

##### Method A.

A mixture of the required **2** and equimolar bromine in acetic acid (1/10 w/v) was refluxed for 2 hours. The solid which separated after cooling was filtered and crystallized from ethanol-ether to give **1** as the hydrobromide (see Table 1).

##### Method B.

To a solution of the required **5** (1 mole) in acetic acid (1/10 w/v), bromine (1 mole) was added dropwise at 70-80°. The solution was then stirred for further 2 hours at 75°. The hydrobromide which separated after cooling was filtered and crystallized from ethanol-ether (see Table 1).

In the case of **1a** the free base was obtained by adjusting an aqueous solution of the salt to pH 4.

When starting from **5d** ( $R = OCH_3$ ), simultaneous bromination of the phenyl ring occurred. This required 100% excess bromine to yield 70% of 3-(3-bromo-4-methoxyphenyl)-4-pyrazoleacetic acid (**1e**).

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- \* To whom correspondence should be addressed.
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