A Facile Synthesis of 3-Aryl-4-pyrazoleacetic Acids and of their 4,5-Dihydro Derivatives

Maria M. Curzu and Gérard A. Pinna

Istituto di Chimica Farmaceutica, Universita' di Sassari,
Via Muroni 23, 07100 Sassari, Italy

Daniela Barlocco and Giorgio Cignarella*

Istituto Chimico Farmaceutico e Tossicologico, Universita' di Milano,
Viale Abruzzi, 42, 20131 Milano, Italy

Received June 13, 1989

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

J. Heterocyclic Chem., **27**, 205 (1990).

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

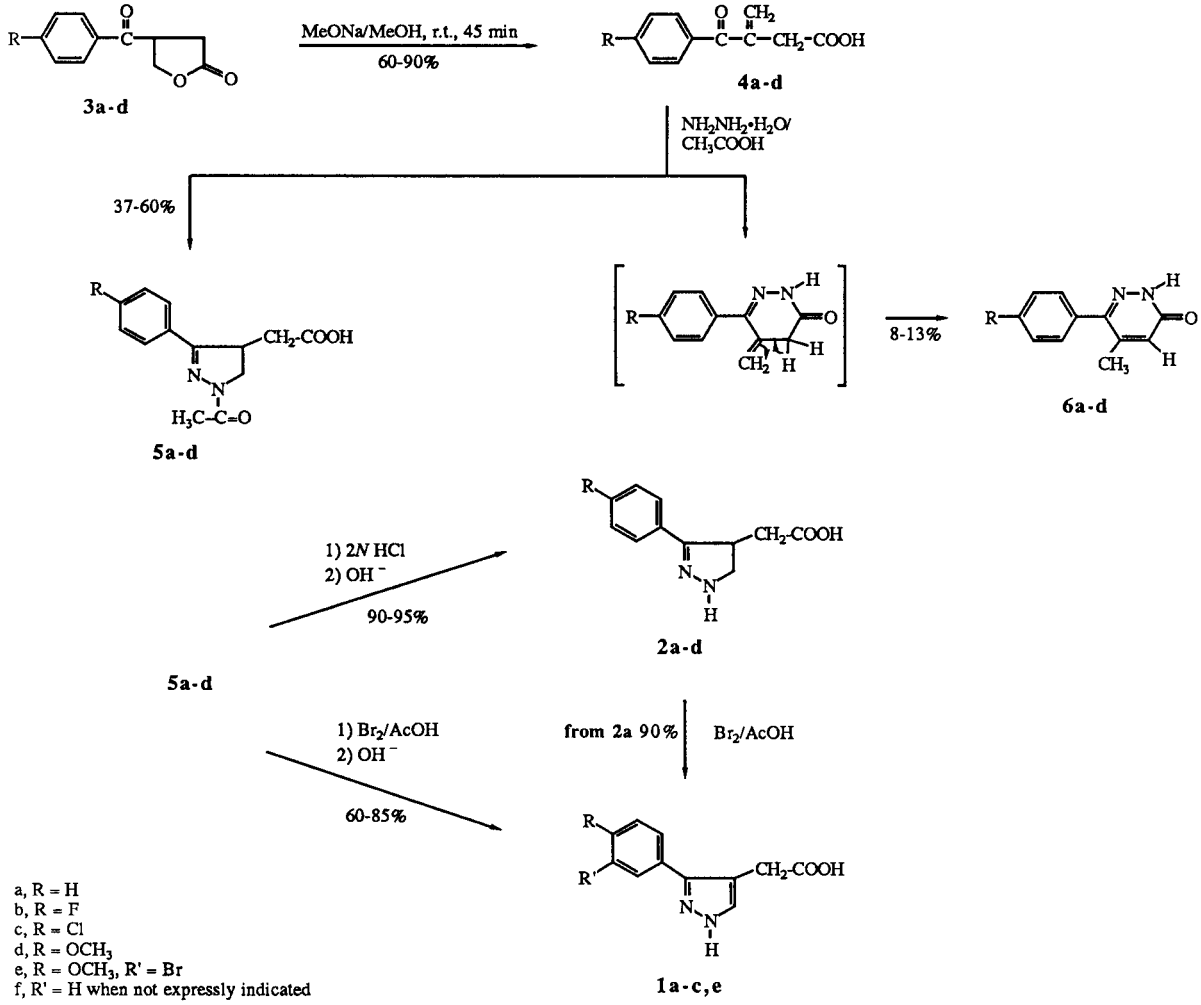

Table 1
Physical Properties and Spectral Data of Compounds **1,2,4,5** and **6** prepared

Compound	R	Yeild %	mp (C°) [a] (solvent)	Molecular Formula or Lit (°C)	^{1}H-NMR (DMSO/TMS) d, J (Hz)
4a	H	60	63-65	60-65 [8]	3.5 (s, 2H, -CH_2-), 5.77- 5.98 (2 app s, 2H, = CH_2), 7.1-8.1 (m, 5H arom), 9.25 (br, s, 1H)
4b	F	87	104-108 (ethanol)	$C_{11}H_9FO_3$ (208.1)	3.5 (s, 2H, -CH_2-), 5.7, 5.95 (2 app s, 2H, =CH_2), 6.9-7.9 (m, 4H arom), 9.25 (br, s, 1H)
4c	Cl	91	88-90 (ethanol)	$C_{11}H_9ClO_3$ (224.5)	3.5 (s, 2H, -CH_2-), 5.8, 6.1 (2 app s, 2H, =CH_2),7.5-7.8 (dd, 4H arom), 9.5 (br, s, 1H)
4d	OCH_3	90	116-119 (ethanol)	$C_{12}H_{12}O_4$ (220.1)	3.5 (s, 2H, -CH_2-), 3.8(s, 3H, OCH_3), 5.69, 5.89 (2 app s, 2H, =CH_2), 6.83-7.75 (dd, 4H arom), 9.4 (br, s, 1H)
5a	H	60	207-210 (ethanol)	$C_{13}H_{14}N_2O_3$ (264.3)	2.1 (s, 3H, CH_3), 2.3 (m, 2H, CH_2COOH), 3.6-3.9 (m, 3H, $CHCH_2$), 7.1-7.5 (m, 5H arom)
5b	F	45	199-202 (ethanol)	$C_{13}H_{13}FN_2O_3$ (264.3)	2.2 (s, 3H, CH_3), 2.6 (m, 2H, CH_2COOH), 3.9-4.1 (m, 3H, $CHCH_2$), 7.0-7.9 (m, 4H arom)
5c	Cl	41	180-182` (ethanol)	$C_{13}H_{13}ClN_2O_3$ (280.2)	2.2 (s, 3H, CH_3), 2.6 (m, 2H, CH_2COOH), 3.9-4.1 (m, 3H $CHCH_2$), 7.0-7.9 (m, 4H arom)
5d	OCH_3	37	190-192 (ethanol)	$C_{14}H_{16}N_2O_4$ (276.2)	2.2 (s, 3H, CH_3), 2.6 (m, 2H, CH_2COCH), 3.8 (s, 3H, OCH_3), 3.9-4.1 (m, 3H, $CHCH_2$), 6.8-7.6 (dd, 4H arom)
6a	H	10	210-212 (ethanol)	218-219 [6]	2.2 (s, 3H, CH_3), 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_3) ,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_3), 7.0 (s, 1H, H-4), 7.3-7.7 (s, 4H arom)
6d	OCH_3	10	202-203 (ethanol)	$C_{12}H_{12}N_2O_2$ (216.2)	2.2 (s, 3H, CH_3), 4.0 (s, 3H, OCH_3), 7.0 (s, 1H, H-4), 7.2-7.6 (dd, 4H arom)
1a	H	78 [b], 90 [c]	220-225 [d] (ethanol-ether)	$C_{11}H_{11}BrN_2O_2$ (283.1)	3.6 (s, 2H, CH_2COOH), 7.3-7.6 (m, 6H, C_6H_5+ H-5)
1b	F	60 [e]	215 dec (ethanol-ether)	$C_{11}H_{10}BrFN_2O_2$ (301.1)	3.55 (s, 2H, CH_2COOH), 6.95-7.85 (m, 5H, C_6H_4 + H-5)
1c	Cl	85 [e]	150 (ethanol-ether)	$C_{11}H_{10}BrClN_2O_2$ (317.1)	3.50 (s, 2H, CH_2COOH), 6.90-7.80 (m, 5H, C_6H_4 + H-5)
1e	2-Br, 4-OCH_3	70 [e]	170 dec (ethanol-ether)	$C_{12}H_{12}Br_2N_2O_3$ (392.1)	3.58 (s, 2H, CH_2COOH), 3.8 (s, 3H, OCH_3), 6.85-7.75 (m, 4H, C_6H_3 + H-5)
2a	H	90	152-154 [f] (ethanol-ether)	$C_{11}H_{13}ClN_2O_2$ (240.7)	2.9 (d, 2H, J = 6, CH_2COOH), 3.65-4.65 (m, 3H, $CHCH_2$), 7.35-7.85 (m, 5H arom)
2b	F	95	177-180 (ethanol-ether)	$C_{11}H_{12}ClFN_2O_2$ (258.6)	2.85 (d, 2H, J = 6, CH_2COOH), 3.6-4.2 (m, 3H, $CHCH_2$), 7.0-7.9 (m, 4H arom)
2c	Cl	90	154-158 (ethanol-ether)	$C_{11}H_{12}Cl_2N_2O_2$ (274.6)	2.85 (d, 2H, J = 6, CH_2COOH), 3.6–4.2 (m, 3H, $CHCH_2$), 7.1-7.9 (m, 4H arom)
2d	OCH_3	91	200-203 (ethanol-ether)	$C_{12}H_{15}ClN_2O_2$ (270.7)	2.9 (d, 2H, J = 6, CH_2COOH), 3.75-4.3 (m, 6H, OCH_3 + $CHCH_2$), 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	%
5a	246.3	63.36	5.68				11.37	Calcd.
		63.12	5.34				11.12	Found
5b	264.2	59.04	4.92			7.19	10.59	
		58.98	4.86			7.05	10.11	
5c	280.2	55.67	4.64		12.49		9.99	
		55.91	4.98		12.25		10.15	
5d	276.2	60.85	5.84				10.14	
		60.85	5.94				10.21	
2a	240.7	54.90	5.44		14.71		11.63	
		54.61	5.40		14.73		11.35	
2b	258.6	51.18	4.65		13.69	7.36	10.85	
		50.97	4.75		13.35	7.06	10.76	
2c	274.6	48.06	4.37		25.49		10.19	
		47.96	4.21		25.23		10.05	
2d	270.7	53.24	5.58		13.09		10.34	
		53.41	5.87		13.21		10.01	
1a	283.1	46.66	3.91	28.25			9.89	
		46.59	3.73	28.00			9.75	
1b	301.1	43.84	3.32	26.56		6.31	9.29	
		43.77	3.23	26.65		6.13	9.35	
1c	317.1	41.63	3.15	25.22	11.03		8.83	
		41.92	3.01	24.95	10.97		8.65	
1e	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 β-aroyl-γ-butyrolactones **3**. Reaction of **3** with equimolar methanolic sodium methoxide gave 3-aroyl-3-butenoic 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 ±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-butenoic Acids **4a-d**.

Compounds were prepared from the appropriate β-benzoyl-γ-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-butenoic 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 *p*H 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 *p*H 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**).

REFERENCES AND NOTES

* To whom correspondence should be addressed.

[1] R. Von Riedel, *Arzneim.-Forsch./Drug Res.*, **31**, 655 (1981).

[2] G. Rainer, U. S. Patent 4,146,721 (1979), Byk-Gulden Lomberg Chemische Fabrik G.m.b.H.; *Chem. Abstr.*, **91**, 20496 (1979).

[3] B. Kohl, European Patent Application EP 94,555 (1983), Byk-Gulden Lomberg Chemische Fabrik G.m.b.H.; *Chem. Abstr.*, **100**, 69874 (1984).

[4] H. Achenbach, G. Rainer and K. Klemm, *Liebigs Ann. Chem.*, **11**, 1919 (1973).

[5] G. Cignarella, D. Barlocco, M. M. Curzu and G. A. Pinna, *Synthesis*, 320 (1989).

[6] D. Barlocco, A. Martini, G. A. Pinna, M. M. Curzu, F. Sala and M. Germini, *Farmaco, Ed. Sci.*, **42**, 585 (1987).

[7] L. C. Behr, R. Fusco and C. H. Jarboe, in "The Chemistry of Heterocyclic Compounds", Vol **22**, Wiley Intersciences, New York, 1967.

[8] G. Cignarella, G. Grella and M. M. Curzu, *Synthesis*, 825 (1980).

[9] J. D. Albright, F. J. McEvoy, D. B. Moran, *J. Heterocyclic Chem.*, **15**, 881 (1978).

[10] W. V. Curran and A. Ross, *J. Med. Chem.*, **17**, 273 (1974).