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SYNTHESIS OF SOME NEW 6-ARYL-4-PYRAZOL-1-YL-PYRIDAZIN-3-ONES AND THE SCREENING OF THEIR ANTIBACTERIAL ACTIVITIES

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SUMMARY

β-aroylacrylic acids (1) react with 3,5-dimethylpyrazole to give α-(disubstituted phenacyl) -3,5-dimethylpyrazol-1-yl acetic acid (2). Reactions of (2) with hydrazine hydrate and phenyl hydrazine afford the corresponding 6-aryl-4-pyrazol-1-yl pyridazinones (3). The behaviour of the pyridazinones with dimethylsulphate, ethyl-bromoacetate, benzoyl chloride, benzenesulfonyl chloride, bromine-acetic acid, phosphorus oxychloride and phosphorus pentasulfide have been described. The reaction of (2) with aldehyde gives the arylidene derivatives. Dehydration of (2) yields the furanone derivative. The *in vitro* antibacterial screening reveals mild activity against Gram-positive for compounds (5 b,c) , while compounds (2*a*) and (3*e*) are inactive.

Recent publications[1,2] dealing with the synthesis and antibacterial screening of pyridazinones revealed that some of these compounds exhibited activities against Gram-positive and Gram-negative. This paper deals with the preparation of a new series of pyridazinones to screen the antibacterial activites of some of these new compounds. The synthesis of various compounds (2–10) are outlined in Scheme 1. Thus the reaction of 2,4-dimethyl (1a) and 3-methyl-4-chloro (1b)-β-aroylacrylic acids with 3,5-dimethylpyrazole in dry benzene gave α-(disubstituted phenacyl)-3,5-dimethylpyrazol-1-yl acetic acids (2a,b) respectively. The structure of the acids (2) were derived from their IR+ spectra which showed υC=O (acid) at 1720, at 1780–1670 υC=O and at 1605–1590 due to υC=N. The PMR (DMSO-d6) spectrum of (2a) exhibited signals at 7.7–7.0 (4H,m.ArH + =CH—), 5.7 (1H,s,OH), 5.3 (1H,t, CH_2=C<u>H</u>), 3.7 (2H,d,CH_2=C<u>H</u>) and 2.25 (12H,s,4CH_1). The PMR (DMSO-d6) spectrum of (2b) exhibited signals at 7.85–7.25 (4H,m,

+ IR λmax in Cm^{-1} and PMR chemical shifts in σ, ppm throughout the paper.

Aril + =CH—), 5.7 (1H,s,OH), 5.28 (1H,t,—CH_2=CH), 3.8 (2H,d, CH_2—CH) and 2.38 (9H,s,3CH_3).

The acids (2a,b) on reaction with hydrazine hydrate and phenylhydrazine yielded the corresponding 6-aryl-4-(3,5-dimethylpyrazol)-4,5-dihydro-3(2H)-pyridazinone (3,ab) and 2,6-diaryl-4-(3,5-dimethyl- pyrazol-1-yl)-4,5-dihydro-3(2H) pyridazinone (3c,d), respectively. The IR spectra of (3a-d) showed υC=O at 1670–1635, υC=N at 1590–1580 in addition to υNH at 3420–330 for compounds (3a,b).

Reaction of (3a,b) with dimethylsulphate, ethylbromoacetate, benzoyl chloride and benzenesulfonyl chloride gave the N-substituted derivatives (3e-i). The IR spectra of (3e-i) showed bands attributable to υC=O at 1660–1640, υC=N at 1590-1580 in addition to υC=O of ester at 1735 for compound (3f) and υSO_2 at 1305–1290 for compounds (3h) and (3i). Structure of (3f) was further established by its reaction with benzylamine in boiling ethanol to give N-benzylcarboxamide derivative (3j), its infrared spectra showed bands at 1660 (υC=O), 1590 (υC=N) and at 3270 (υNH).

In the present investigation, it was found that treatment of (3a) with bromine-acetic acid mixture afforded compounds (4). The formation of this compound can be mechanistically explained on the basis that the first step is dehydrogenation, followed by addition of bromine on the formed double bound and then elimination of hydrogen bromide, in a similar manner to that observed in the bromination of pyrazolines[3], to afford compound (4). Its infrared spectra showed bands at 1690 (υC=O), 1640 (υC=N) and 3490 (υNH).

This work investigated the behaviour of the pyridazinone (3a,b) towards nucleophilic reagents like phosphorus oxychloride. Thus, compounds (3a,b) when allowed to react with phosphorus oxychloride, the chloropyridazine derivatives (5a,b) was obtained. The IR spectra of (5) were devoid of υC=O. The behaviour of the resulting 3-chloropyridazine towards different reagents has been described.

Reaction of (5b) with phenylhydrazine in ethanol gave the 3-phenylhydrazine derivative (c). The IR spectra of (5c) showed bands attributable to υC=N, υNH at 1590 and 3410, respectively.

Reaction of (5a) with p-toluidine gave the 3-substituted derivative (5d). The IR spectra of (5d) showed bands attributable to υC=N at 1610 and 3430 for υNH.

Anthranilic acid reacted with (5b) at 150°C to give (2-(3-methyl-4-chlorophenyl)-4-(3,5-dimethylpyrazol-1-yl)-3,4-dihydro-10 H-pyridazino (6,1-b) quinazolin -10-one (6). The IR spectra of (6) showed a band at 1725 (υC=O) and two bands for (υC=N) at 1655 and 1625.

Chloropyridazines (5a,b) react with benzoylhydrazine in refluxing n-butanol to give the triazolopyridazine derivatives (7a,b). The structure of triazole derivatives were proved from its IR spectra which exhibit bands at 1590–1580 attributable to υC=N.

The pyridazinones (3a,b) reacted with phosphorus pentachloride in dry xylene to give the pyridazine thione derivatives (8a,b) respectively, a reaction in which thionotion together with dehydrogenation takes place[1]. The infrared spectra of (8a,b) exhibited characteristic absorption bands for (υN—C=S) at 1460, (υC=S) at 1590–1595 and (υ(NH) at 3440–3420. The PMR ($CDCl_3$) spectrum of (8b) exhibited signals at 8.5–7.7 (5H, m,Ar—H + =CH— + =CH—) and 2.6 (9H,S,3CH_3).

The thione (8a,b) reacts with benzylamine and yields the Schiff bases (8c,d) which show infrared absorption bands at 1590–1580 for υC=N and at 3420–3390 for υNH. Also thione (8b) reacts with hydrazine hydrate in ethanol and yields the hydrazone derivative (8e).The IR spectra of (8e) showed bands at 1585 for υC=N and at 3400 due to υNH.

Interestingly, compounds (2a,b) were condensed with p-chlorobenzaldehyde in boiling ethanol with a few drops of piperidine to give the corresponding α-(3,5-dimethylpyrazol-1-yl)-β-(p-chlorobenzyl-idene)-β-aroylpropionic acids (9a,b). The IR spectra of (9) exhibited two υC=O bands in the region 1670–1635 and 1720, indicating the presence of ketone carbonyl and carboxyl group respectively.

Compound (2b) easily dehydrated by boiling with acetic anhydride or heating at its melting point to yield the furanone derivative (10). The structure of (10) was established from the following facts:

a) It is insoluble in aqueous alkali.

b) It is readily hydrolysed by hot alkali giving the corresponding acid (2b).

c) The IR spectra of (10) shows strong absorption band at 1780 characteristic of five membered lactone.

d) Compound (10) reacts with hydrazine hydrate in boiling ethanol to give (3b), which was identified by its IR spectra and its melting point.

Screening for an antibacterial activity:

The prepared compounds (2a), (3e), (5b,c) were tested for in vitro antibacterial activity using the method described by Heatly(5). The medium for screening was composed of (g 11000 ml) "Lab-lemco" beef extract, 1,0; yeast extract (Oxoid L 20), 2.0; peptone (Oxoid L 37), 5.0; sodium chloride, 2.0 and agar (pH 7.0).

Cylinders of known volume (0.1 ml) were placed on the solid medium needed with a Gram-positive or a Gram-negative test organism. A known constant volume (0.05 ml) of the appropriate compound (2a), (3e) and (5b,c) were dissolved in sodium dodecyl sulfate (SDS), introduced into each cylinder and allowed to diffuse through the agar at room temperature for one hour and finally at 37°C for about 18–20 hrs. Clear circular zones of inhibition of the test organisms were formed around the holes containing compounds (5b) and (5c). It is suggested that (5b) (5c) possess mild activites against Gram-positive as shown in Table 1.

Table 1. *In vitro* antibacterial activities of some of the prepared compounds.

Compound.	Staph epideroridis	E.Coli	P. auregonosa.
2*a*	—	–	–
3*e*	—	–	–
5b	+	–	–
5*c*	+	–	–

– The width of the zone unhibition indicates the potency of antibacterial activity.
(—) no antibacterial activity.
(+) mild activity with the diameter of the zone equal to 1 cm.

EXPERIMENTAL

All melting points were uncorrected. The IR spectra (KBr) were recorded on a Unicam SP 1200 spectrophotometer and PMR spectra on Varian VN 1009 (S-60 T) instrument using TMS as internal standard. Reaction of (1a, b) with pyrazole; formation of (2a,b):

To a solution of (1a,b) (0.01 mole) in dry benzene (20 ml), 3,5–dimethylpyrazole (0.01) mole was added and the reaction mixture refluxed for 10 hrs. The solid that separated on cooling was crystallized from a suitable solvent to give (2a, b) respectively.

Reaction of (2a,b), (3f), (5a,b), (8a,b) and (10) with hydrazines, amines and benzoylhydrazine; formation of (3a-d), (3j), (5c,d), (7a,b) and (8c-e):

A mixture of (2a,b), (3f), (5a,b), (8a,b) or (10) (0.01 mole) and hydrazine hydrate, phenylhydrazine, benzylamine, p-toluidine or benzoylhydrazine (0.01 mole) in ethanol or butanol (20 ml) was refluxed for 6 hrs. The solid that separated on cooling was crystallized from the suitable solvent to give (3a-d), (3j), (5c,d), (7a,b) and (8c,e). (See Table 2).

Reaction of (3a,b) with dimethylsulfate, ethylbromoacetate, benzoyl chloride and benzenesulfonyl chloride; formation of (3e-i):

A mixture of (3a,b) (0.01 mole), anhydrous potassium carbonate (0.03 mole), dimethylsulfate, ethylbromoacetate, benzoylchloride or benzenesulfonyl chloride (0.03 mole) and dry acetone (50 ml) were refluxed for 20 hours. After removing the excess solvent, the products were crystallized from the proper solvent to give compounds (3e-i). (see Table 2).

Action of bromine-acetic acid mixture on (3a); formation of (4):

The solution of (3a) (0.01 mole) in glacial acetic acid (20 ml) was stirred and treated portionwise with bromine at 60–70°C. The solution was further stirred for 2 hrs, then cooled in ice. The precipitated product was filtered off, washed with light petroleum (40–60°C), stirred with concentrated ammonium hydroxide for 15 minutes. The solid product was crystallized from a suitable solvent to give (4). (Table 2).

Reaction of (3a,b) with $POCl_3$; formation of (5a, b):

A mixture of (3a,b) (0.01 mole) and $POCl_3$ (10 ml) was gently refluxed for 30 minutes, cooled, treated with crushed ice and the precipitated solid was filtered and crystallized from a suitable solvent to give (5a,b) respectively (Table 2).

Reaction of (5b) with anthranilic acid; formation of (6):

A mixture of (5b) (0.01 mole) and anthranilic acid (0.01 mole) was heated in an oil-bath at 150°C for 1 hour, cooled and treated with ethanol. The solid obtained was crystallized from a suitable solvent to give (6) (Table 2).

Action of P_2S_5 on (3a,b); formation of (8a, b);

A solution of (3a, b) (0.01 mole), P_2S_5 (0.01 mole) and dry xylene (50 ml) was boiled under reflux for 6 hrs. The reaction mixture was filtered while hot and then concentrated. The product which separated on cooling was crystallized from a suitable solvent to give (8a,b) respectitively (Table 2).

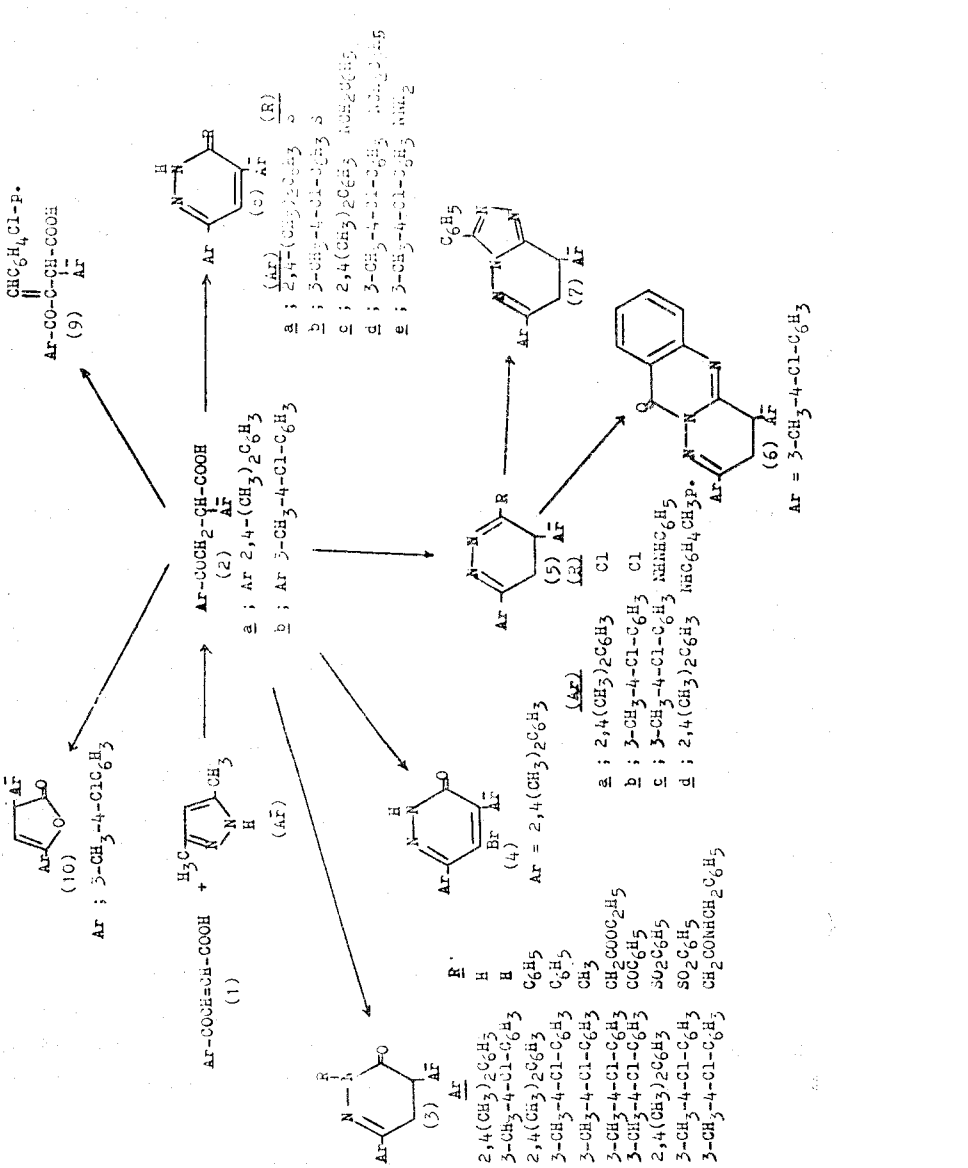
Ar-COCH=CH-COOH
(1)
(4Ar')
Ar-COCH2-CH-COOH
(2)
a ; Ar 2,4-(CH3)2C6H3
b ; Ar 3-CH3-4-Cl-C6H3
(10)
Ar ; 3-CH3-4-ClC6H3
CHC6H4Cl-p.
Ar-CO-C-CH-COOH
(9)
(3) Ar
(4)
Ar = 2,4(CH3)2C6H3
(5) Ar
(7) Ar
(6) Ar
Ar = 3-CH3-4-Cl-C6H3
(Ar')
a ; 2,4-(CH3)2C6H3
b ; 3-CH3-4-Cl-C6H3
c ; 2,4(CH3)2C6H3
d ; 3-CH3-4-Cl-C6H3
e ; 3-CH3-4-Cl-C6H3
(R)
O
NHC6H5
NHC6H4CH3p.

Table 2. Physical and analytical data of various compounds prepared.

Compound.	m.P°C	Solvent. Yield %	M. Formula. M. Wt.	Analysis % (Found/Calc.)		
				C	H	N
2a	175	Benzene	$C_{17}H_{20}N_2O_3$	68.20	6.90	9.10
–		96	300	68.00	6.67	9.33
2b	173	Benzene	$C_{16}H_{17}ClN_2O_3$	60.20	5.20	8.70
–		94	320.5	59.91	5.30	8.74
3a	198	butanol	$C_{17}H_{20}N_4O$	69.10	6.40	18.80
–		87	296	68.92	6.72	18.92
2b	225	butanol	$C_{16}H_{17}ClN_4O$	60.30	4.90	17.70
–		92	316.5	60.66	5.37	17.69
3c	133	L.P. (60–80)	$C_{23}H_{24}N_4O$	74.20	6.40	14.90
–		83	372	74.19	6.45	15.05
3d	143	Ethanol	$C_{22}H_{21}ClN_4O$	67.40	5.30	14.20
–		86	392.5	67.26	5.35	14.27
3e	125	L.P. (60–80)	$C_{17}H_{19}ClN_4O$	61.80	5.50	17.20
–		60	330.5	61.72	5.75	16.94
3f	96	L.P. (60–80)	$C_{20}H_{23}ClN_4O_3$	59.50	5.90	14.10
–		63	402.5	59.63	5.71	13.91
3g	231	Ethanol	$C_{23}H_{21}ClN_4O_2$	65.80	4.90	13.50
–		57	420.5	65.64	4.99	13.32
3h	100	Methanol	$C_{23}H_{24}N_4O_3S$	63.50	5.50	12.90
–		72	436	63.30	5.50	12.84
3i	238	Ethanol	$C_{22}H_{21}ClN_4O_3S$	57.90	4.40	12.20
–		64	456.5	57.83	4.60	12.27
3j	171	Ethanol	$C_{25}H_{26}ClN_5O_2$	64.70	5.60	15.20
–		80	463.5	64.72	5.61	15.10
4	130	L.P. (60–80)	$C_{17}H_{17}BrN_4O$	54.80	4.60	15.00
		55	373	54.69	4.56	15.01
5a	128	L.P. (60–80)	$C_{17}H_{19}N_4Cl$	64.70	5.90	17.80
–		540	314.5	64.86	6.04	17.81
5b	176	Ethanol	$C_{16}H_{16}Cl_2N_4$	57.30	4.78	16.72
–		38	335	57.31	4.78	16.72
5c	158	Ethanol	$C_{22}H_{23}ClN_6$	65.10	5.60	02.70
–		61	406.5	64.94	5.66	20.66
5d	202	Ethanol	$C_{24}H_{27}N_5$	74.80	7.10	18.30
–		63	385	74.81	7.01	18.18
6	173	Ethanol	$C_{23}H_{20}ClN_5O$	66.30	4.50	16.70
		72	417.5	66.11	4.79	16.77
7a	183	Ethanol	$C_{24}H_{24}N_6$	72.80	5.90	21.30
–		48	396	72.73	6.06	21.21
7b	205	Ethanol	$C_{23}H_{21}ClN_6$	66.20	5.00	20.30
–		45	416.5	66.27	5.04	20.17
8a	182	L.P. (60–80)	$C_{17}H_{18}N_4S$	65.60	5.70	17.90
–		63	310	65.81	5.81	18.06
8b	220	Ethanol	$C_{16}H_{15}ClN_4S$	58.10	4.50	16.70
–		60	330.5	58.09	4.54	16.94
8c	194	Ethanol	$C_{24}H_{25}N_5$	75.30	6.50	18.40
–		52	383	75.20	6.53	18.28
8d		Ethanol	$C_{23}H_{22}ClN_5$	64.20	5.60	17.40
–	214	48	403.5	68.40	5.45	17.35
8e		Ethanol	$C_{16}H_{17}ClN_6$	58.50	5.30	25.70
–	180	45	328.5	58.45	5.18	25.57
9a		Ethanol	$C_{24}H_{23}ClN_2O_3$	68.30	5.50	6.60
–	171	56	422.5	68.17	5.44	6.63
9b		Ethanol	$C_{23}H_{20}Cl_2N_2O_3$	62.30	4.60	6.10
–	180	52	442	62.30	4.51	6.32
		Butanol	$C_{16}H_{15}ClN_2O_2$	63.50	5.10	9.30
10	245	63	302.5	63.47	4.96	9.26

Condensation of acid (2a,b) with p-chlorobenzaldehyde; formation of (9a, b):

A solution of (2a,b) (0.01 mole), p-chlorobenzaldehyde (0.01 mole), piperidine (few drops) in ethanol (30 ml) was refluxed for 4 hrs. The solid separated after cooling was crystallized from a suitable solvent to give (9a,b), respectively (Table 2).

Conversion of acid (2b) to furanone (10):

Method A: A solution of acid (2b) (0.01 mole) in acetic anhydride (20 ml) was refluxed for 4 hrs. The solid obtained after concentration and cooling was crystallized from a suitable solvent to give furanone (10).

Method B: The acid (Cb) (0.01 mole) was heated at its melting point for 30 minutes and the resulting solid was crystallized from a suitable solvent to give the furanone (10) (Table 2).

Hydrolysis of furanone; formation of the acid (2b):

A solution of furanone (10) (1 g) in ethanol (10 ml) was treated with sodium hydroxide (1 g. in 5 ml water), then heated under reflux for 2 hrs. The cooled solution was acidified with dilute hydrochloric acid and the precipitate was crystallized from a suitable solvent and identified as (2b) by melting point and mixed melting point determination.

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