Synthesis and Reactions of Some New Pyridazinones

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Summary: β(p-Chlorobenzyl) acrylic acid (**1**) reacts with 3-methyl-1-phenyl-2-pyrazolin-5-one to give the adduct (**2**). Reactions of (**2**) with hydrazine hydrate and phenylhydrazine afford the corresponding 4-pyrazolinonyl- pyridazinones (**3a** and **b**). Reactions of 4-pyrazolinonyl-pyridazinone (**3a**) with dimethylsulphate, diethylsulphate, ethyl bromoacetate, benzenesulphonyl chloride, anisaldehyde, phenylmagnesium bromide and bromine - acetic acid mixture have been described. Reaction of (**3a**) with $POCl_3$ yield the dichloro derivative (**7a**), the behaviour of the dichloro derivative towards sodium methoxide, hydrazine hydrate, anthranilic acid and sodium azide has been investigated.

Introduction

As a continuation of the recent studies [1,2] new series of pyridazinones have been prepared through the addition of 3-methyl-1-phenyl-2-pyrazoline-5-one to β-(p-chlorobenzoyl)acrylic acid followed by cyclization of the adduct to give the corresponding 4-pyrazolinonyl-pyridazinones. The synthesis of various compounds (**1-11**) are outlined in Scheme 1.

Thus, the reaction of β-(p-chlorobenzoyl) acrylic acid (**1**) with 3-methyl-1-phenyl-2-pyrazoline-5-one in dry benzene gave 4,5-dihydro- α-[2-(4-chlorophenyl)-2-oxoethyl]-3-methyl-5-oxo-1-pheny l-1H-pyrazole-4-acetic acid (**2**).

The reaction of the acid (**2**) with hydrazine hydrate or phenylhydrazine in boiling ethanol yielded 6(p-chlorophenyl)-4-pyrazolinonyl-1,2,3,4, 5-tetrahydropyridazin-3-one (3a) and 6(p-chloro phenyl)-2-phenyl-4-pyrazolinonyl-2,3,4,5-tetra hydropyrida-zin-3-one (3b).

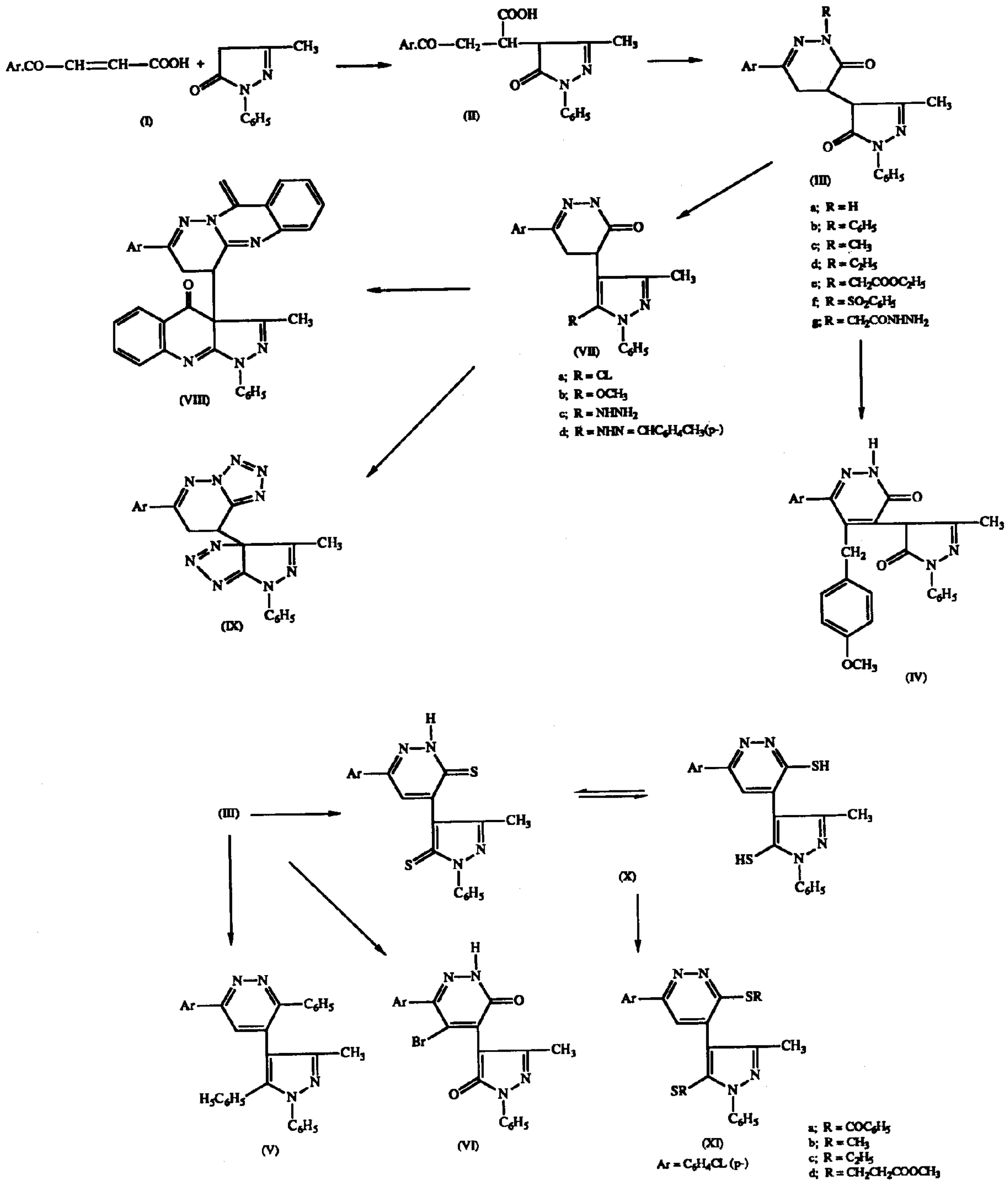
Reaction of (3a) with dimethylsulphate, diethylsulphate, ethyl bromoacetate and benzenesulfonyl chloride gave the N-substituted products (**3c-f**). The structure of (**3e**) was further established by its reaction with hydrazine hydrate in boiling ethanol to give the hydrazide (**3g**).

Condensation of (3a) with anisaldehyde in the presence of ethanolic KOH took place at the 5-position [1] to give the 4,5,6- trisubstituted-pyridazin-3-one (**4**).

Reaction between phenylmagnesium bromide and the pyridazinone (3a) gave compound (**5**) found by 1,2-addition to the two carbonyl groups followed by elimination of two molecules of water and subsequent spontaneous dehydrogenation. This is in accordance with the result obtained by Sayed *et al.* [1].

In the present investigation it was found that treatment of (3a) with bromine - acetic acid mixture afforded compound (**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 bond and then elimination of hydrogen bromide in a similar manner to that observed in the bromination of poyrazolines [3] to afford compound (**6**).

This work reports on the behaviour of the pyridazinone derivatives towards nucleophilic reagents like phosphorus oxychloride. Treatment of (**3a**) with $POCl_3$ gave the dichloro derivative (**7a**). The dichloro derivative (**7a**) reacts with sodium methoxide to give the dimethoxy derivative (**7b**).


(I)
(II)
(III)
a; R = H
b; R = C_6H_5
c; R = CH_3
d; R = C_2H_5
e; R = $CH_2COOC_2H_5$
f; R = $SO_2C_6H_5$
g; R = $CH_2CONHNH_2$
(IV)
(VII)
a; R = CL
b; R = OCH_3
c; R = $NHNH_2$
d; R = NHN = $CHC_6H_4CH_3$(p-)
(VIII)
(IX)
(III)
(X)
(V)
(VI)
(XI)
Ar = C_6H_4CL (p-)
a; R = COC_6H_5
b; R = CH_3
c; R = C_2H_5
d; R = $CH_2CH_2COOCH_3$

Reaction of (7a) with hydrazine hydrate in absolute ethanol gave the dihydrazino derivative (7c). Compound (7c) condensed, with aromatic aldehyde namely p-tolualdehyde in boiling ethanol and yielded the diimine derivative (**7d**).

Anthranitic acid reacted with (7a) to give compound (**8**).

The reaction of the dichloro derivative (**7a**) with sodium azide give compound (**9**). An alternative route for the preparation of compound (9) is the reaction of the dihydrazino derivative (7c) with nitrous acid to give the same compound (9). The similarity of these compounds were identified by IR and by mixed melting points determination with the sample prepared before.

Compound (3a) reacted with phosphorus pentasulphide in dry xylene to give the dithio derivative (10), a reaction in which thionation together with dehydrogenation takes place [4]. Compound (10) evidently exists in the mercapto-thioamide equilibrium.

Treatment of (10) with benzoyl chloride, dimethylsulphate, diethylsulphate in dry acetone yielded the corresponding 5- substituted derivatives (**11a-c**), respectively.

Compound (10) reacts also with methyl acrylate to give the diadduct compound (**11d**).

Experimental

All melting points are uncorrected IR (KBr discs) recorded on a Unicam SP 1200 spectrophotometer. The PMR spectra on a Jeol F x 100 Fourier transform instrument using tetramethyl silane as internal standard.

Reaction of (1) *with pyrazolinones: Formation of the* (2)

To a solution of (1) (0.01 mole) in dry benzene (20 ml), 3-methyl-1-phenyl-2-pyrazolin-5-one (0.01 mole) was added and the reaction mixture reflexed for 10 hrs. The solid that separated on cooling was crystallized from ethanol to give (2), m.p. 242°; IR 1710 (C=O, acid), 1645 (C=O) and 1595 (C=N); PMR (DMSO-d_6) δ 8.1-7.25 (9H, m, Ar-H), 4.23-3.15 (4H, m, CH_2-CH + COCH) and 2.29 (3H, s, CH_3). (Found: C, 62.61; H, 4.3; N, 7.4 $C_{20}H_{17}ClN_2O_4$ requires: C, 62.41; H, 4.42; N, 7.28).

Reaction of (**2**), (**3a**), (**3e**), (**7a**) *and* (**7c**) *with hydrazines and aromatic aldehydes: Formation of* (**3a**), (**3b**), (**4**), (**3g**), (**7c**) *and* (**7d**)

To a solution of (**2**), (**3a**), (**3e**), (**7a**), or (**7c**) (0.01 mole) in ethanol or absolute ethanol (20 ml), hydrazine hydrate, phenylhydrazine, benzaldehyde or tolualdehyde (0.01 or 0.02 mole) was added and the reaction mixture refluxed for 5 hrs. The solid that separated on cooling was crystallized from acetic acid (**3a**), (**7d**), ethanol (**3b**), (**4**), (**3g**) or benzene (**7c**).

(**3a**) m.p. 193°; IR 1650 (C=O), 1590 (C=N) and 3380 (NH). (Found: C, 62.9; H, 4.6; N, 14.8 $C_{29}H_{17}ClN_4O_2$ requires: C, 63.07; H, 4.46; N, 14.71). (**3b**) m.p. 113°; IR 1625 (C=N): 1575 (C=N). (Found: C, 69.6; H, 4.3; N. 12.5 $C_{26}H_{21}ClN_4O_2$ requires: C, 68.34; H, 4.6; N, 12.26). (**3g**) m.p. 201°, IR 1635 (C=O): 1580 (C=N) and 3400 (NH). (Found: C, 58.6; H, 4.6; N, 18.2 $C_{22}H_{21}ClN_6O_3$ requires: C, 58.34; H, 4.64; N, 11.23). (**7c**) m.p. 160°, IR C=N (1610) and 3300 (NH). (Found: C, 58.6; H, 5.2; N, 27.2 ($C_{20}H_{21}ClN_8$ requires: C, 58.75; H, 5.14; N, 27.41). (**7d**) m.p. 300°, IR 1585 (C=N) and 3160 (NH)(. (Found: C, 70.9; H, 5.5; N. 18.5 $C_{36}H_{33}ClN_8$ requires: C, 70.53; H, 5.38; N, 18.28).

Reaction of (3a) *and x with dimethylsulphate, diethylsulphate, ethyl bromoacetate, benzoyl chloride and benzenesulfonyl chloride: Formation of* (**3c-f**) *and (*(**11a-c**)

A mixture of (3a) or (10) (0.01 mole), anhydrous potassium carbonate (0.03 mole), dimethyl -sulphate, diethylsulphate, ethyl bromoacetate, benzoyl chloride or benzenesulfonyl chloride (0.03 mole) and dry acetone (50 ml) was refluxed for 20 hrs. All removing the excess solvent, the products were crystallized from benzene (**3c, 3d, 11a**), bezene/pet.ether 40-60° (**3e**), ethanol (**3f**) and pet.ether 80-100° (**11b,11c**).

(**3c**) m.p. 256°; IR 1640 (C=O), 1600 (C=N). (Found: C, 63.5; H, 4.7; N, 14.3 $C_{21}H_{19}ClN_4O_2$ requires: C, 63.87; H, 4.81; N, 14.19). (**7d**) m.p. 213°; IR 1640 (C=O), 1585 (C=N). (Found: C, 64.5; 5.2;

N, 13.8 $C_{22}H_{21}ClN_4O_2$ requires C, 64.62; H, 5.14; N, 13.70). (3e) m.p. 83°; IR 1725 (C=O, ester), 1660 (C=O), 1580 (C=N). (Found: C, 61,7; H, 4.6; N, 11.9 $C_{24}H_{23}ClN_4O_4$ requires: C, 61.73; H, 4.93; N, 12.00). **(3f)** m.p. 265°; IR 1640 (C=O), 1570 (C=N). (Found: C, 60.1; H, 4.3; N, 10.5 $C_{26}H_{23}N_4O_4SCl$ requires: C, 59.94; H, 4.03; N, 10.75). **(11a)** m.p. 196°; IR 1670 (C=O), 1595 (C=N). (Found: C, 66.2; H, 3.8; N, 8.8 $C_{34}H_{23}ClN_4O_2S_2$ requires: C, 65.96; H, 3.71; N, 9.05). **(11b)** m.p. 172°; IR 1590 (C=N), (Found: C, 60.4; H, 4.3; N, 12.4 $C_{22}H_{19}ClN_4S_2$ requires: C, 60.20; H, 4.33; N, 12.77). **(11c)** m.p. 153°; IR 1595 (C=O); PMR (DMSO-d_6) δ 8.1-7.12 (10 H.m. ArH + -CH), 4.48 (4H, q, 2xCH$_2$ or ethyl), 3.12 (3H, s, CH$_3$) and 1.34 (6H, t, 2 x CH$_3$ of ethyl). (Found: C, 61.6; H, 5.1; N, 12.0 $C_{24}H_{23}ClN_4S_2$ requires: C, 61.73; H, 4.93; N, 12.00). **(3f)** m.p. 265°; IR 1640 (C=O), 1570 (C=N)O. (Found: C, 60.1; H, 4.3; N, 10.8 $C_{26}H_{21}N_4O_4SCl$ requires; C, 59.94; H, 4.03; N, 10.75). **(11a)** m.p. 196°; IR 1670 (C=O), 1595 (C=N). (Found; C, 66.2; H. 3.8; N, 8.8 $C_{34}H_{23}ClN_4O_2S_2$ requires C, 65.96; H, 3.71; N, 9.05). **(11b)** m.p. 172°; IR 1590 (C=N). (Found: C, 60.4; H, 4.3; N, 12.4 $C_{22}H_{19}ClN_4S_2$ requires: C, 60.20; H, 4.33; N, 12.77). **(11c)** m.p. 1543°; IR 1595 (C=O); PMR (DMSO-d_6) δ 8.1-7.2 (10 H.m. ArH + -CH), 4.48 (4H, q, 2xCH$_2$ of ethyl), 3.12 (3H, s, CH$_3$) and 1.34 (6H, t, 2xCH$_3$) of ethyl). (Found: C, 62.6; H, 5.1; N, 12.0 ($C_{24}H_{23}ClN_4S_2$ requires: C, 61.73; H, 4.93; N, 12.00).

Action of Grignard reagent on **(3a)***: Formation of* **(5)**

The solution of phenyl magnesium bromide (prepared from 0.03 mole of bromobenzene and 0.03 atoms of magnesium) was added to a solution of (3a) (0.01 mole) in dry ether (100 ml). The solution obtained was refluxed for 4 hrs. in a boiling water bath and left overnight. The reaction mixture was the hydrolysed with saturated solution of ammonium chloride, extracted with ether, and the solvent removed to give a solid product which was crystallized from benzene to give (5), m.p. 271°; IR 1580 (C=N). (Found: C, 77.3; H, 4.6; N, 11.0 $C_{23}H_{23}ClN_4$ requires: C, 77.03; H, 4.61; N, 11.23).

Action of bromine m- acetic acid mixture on (3a)*: Formation of* (6)

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 conc. ammonium hydroxide for 15 minutes. The solid product was crystallized from acetic acid to give (6), m.p. 206°; IR 1670 (C=O), 1580 (C=N), 3200 (NH). (Found: C, 52.6; H, 3.2; N, 12.1 $C_{20}H_{14}BrClN_4O_2$ requires: C, 52; 45; H, 3.06; N, 12.24).

Reaction of (3a) *with* $POCl_3$*: Formation of* (7a):

A mixture of (3a) (0.01 mole) and $POCl_3$ (10 ml) was gently refluxed for 30' minutes, cooled, treated with crushed ice and the precipitated solid filtered and crystallized from benzene to give VIIa, m.p. 199°; IR 1585 (C=N). (Found: C, 57.4; H, 3.5; N, 13.2 $C_{20}H_{15}Cl_3N_4$ requires: C, 57.48; H, 3.59; N, 13.41).

Reaction of (7a) *with sodium methoxide: Formation of* (7b)

The dichloro compound (7a) (0.01 mole) was added to sodium methoxide solution [from sodium (0.02 mole) in absolute methanol (50 ml).]. The mixture was refluxed for 2 hrs., then evaporated under reduced pressure. To the residue was added water (10 ml) and insoluble matter was filtered off and crystallized from a suitable solvent to give (7b), m.p. 161°; IR 1595 (C=N). (Found: C, 64.5; H, 5.1; N, 13.4 $C_{22}H_{21}ClN_4O_2$ requires C, 64.62; H, 5.14; N, 13.7).

Reaction of (7a) *with anthranilic acids: Formation of* (8)

A mixture of (7a) (0.01 mole) and anthranilic acid (0.02 mole) was heated in an oil-bath at 150°C for 1 hour, cooled and triturated with ethanol. The solid obtained was crystallized from DMF to give (8), m.p. 292°; IR 1695 (C=O), 1625 (C=N). (Found: C, 70.3; H, 3.9; N, 14.5 $C_{34}H_{23}ClN_6O_2$ requires: C, 70.04; H, 3.94; N, 14.42).

Reaction of (7a) *with sodium azide: Formation of* (9)

A mixture of (7a) (1 gm), sodium azide (2 gm), water (5 ml) and dimethylformamide (20 ml) was boiled for 2 hrs, and cooled. The solid obtained upon dilution with water was filtered and crystallized from ethanol to give (9), m.p. 212°; IR 1580 (C=N). (Found: C, 58.3; H, 3.3; N, 34.4 $C_{20}H_{15}ClN_{10}$ requires C, 58.46; H, 3.65; N; 34.01).

Reaction of (7c) *with nitrous acid: Formation of* (9)

An aqueous solution of $NaNO_2$ (0.03 mole in 10 ml H_2O) is added dropwise with stirring to a solution of (7c) (0.01 mole) in 4 N acetic acid (10 ml) and stirring is continued for 1 hr. The solid formed is filtered and crystallized from ethanol to give (9).

Action of P_2S_5 on (3a): *Formation of* (10)

A solution of (3a) (0.01 mole), P_2S_5 (0.03 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 benzene to give (9), m.p. 230°; IR 1385 (C=S), 1475 (N-C=S), 1595 (C=N), 3120 (5H). (Found: C, 58.4; H, 3.8; 13.7 $C_{20}H_{15}ClN_4S_2$ requires: C, 58.46; H, 3.65; N, 13.64).

Reaction of (10) *with methyl acrylate: Formation of* (11d)

A mixture of (10) (0.01 mole) and methyl acrylate (0.02 mole) in ethanol (20 ml) is treated with few drops of 10% sodium hydroxide solution and the mixture heated under reflux for 12 hrs. The solid formed after cooling was crystallized from pet.ether 80- 100° to give (11d), m.p.m 84°; IR 1720 (C=O, ester), 1600 (C=N); (Found: C, 57.6; H, 4.8; N, 9.5 $C_{28}H_{27}ClN_4O_4S_2$ requires: C, 57.68; H, 4.63; N, 9.61).

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