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SYNTHESIS AND REACTIONS OF 4-[3-OXO-1-PHENYL-3-(P-SUBSTITUTED PHENYL)-PROPYL]-1-[4-CHLORO-PHENYL)-2-(3-METHYL-5-OXO-2-PYRAZOLIN-1-YL) THIAZOLE

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Compounds 4-[3-oxo-1-phenyl-3-(p-chloro or p-methoxyphenyl)-propyl]-1-[4-chlorophenyl)-2-(3-methyl-5-oxo-2-pyrazolin-1-yl)]-thiazole (II a-b) have been prepared. The reactions of compounds (II a-b) with hydrazines in ethanol and in acetic acid, hydroxylamine hydrochloride, aromatic aldehydes, zinc dust, Grignard reagents, P_2S_5 and polyphosphoric acid have been investigated.

Key words. Michael Adducts, Thiazoles pyrazolone Derivatives.

Introduction

Substituted pyrazolones and their applications as antibacterial [1] herbicidal [2] and potent analgesic agents have received considerable attention in recent years. Besides, they were shown to be much less toxic than Dipyrone [3] (Novalgin). Pyrazoles possess antibacterial [4] and virucidal activities against encephlomyocarditis virus [5]. Pyrazolothiazoles also have been reported to possess antibacterial activity [6]. This promoted us to synthesize some new pyrazolone derivatives through the nucleophilic addition of 4-(p-chlorophenyl)-2-(3-methyl-5-oxo-2-pyrazolin-1-yl)thiazole (1) to chalcones i.e. benzal p-chloroacetophenone and/or benzal p-methoxy acetophenone and to study the behavior of the adducts [1,7-10] towards different reagents. The synthesis of the new compounds are outlined in Scheme-1.

Experimental

All melting points are uncorrected. I.R. spectra were recorded on Beckman spectrophotometer. The 1HNMR spectra were run on a varian A_{90} standard equipment using TMS as an internal standard.

Preparation of 4'-(p-chlorophenyl)-2-(3-methyl-5-oxo-2-pyrazolin-1-yl)thiazole(1) A mixture of 0.01 mole of 4-(p-chlorophenyl) thiazole and 0.02 mole of hydrazine hydrate in 60 ml. ethanol was refluxed for 6 hr. The solid obtained after concentration and cooling was recrystalized from the proper solvent to give compound (1).

Reaction of compound (1) with benzal (4-chloro or 4-methoxy) acetophenone:- Formation of Michael adducts (II a-b). A mixture of pyrazolone derivative (1) (0.01 mole) and benzal (4-chloro or 4-methoxy) acetophenone (0.01 mole) in ethanol (40 ml) in presence of few drops of piperidine was heated under reflux for 6 hr. The solid obtained after cooling was crystallized from the suitable solvent (Table 1).

Condensation of compounds (II a-b) with hydrazines

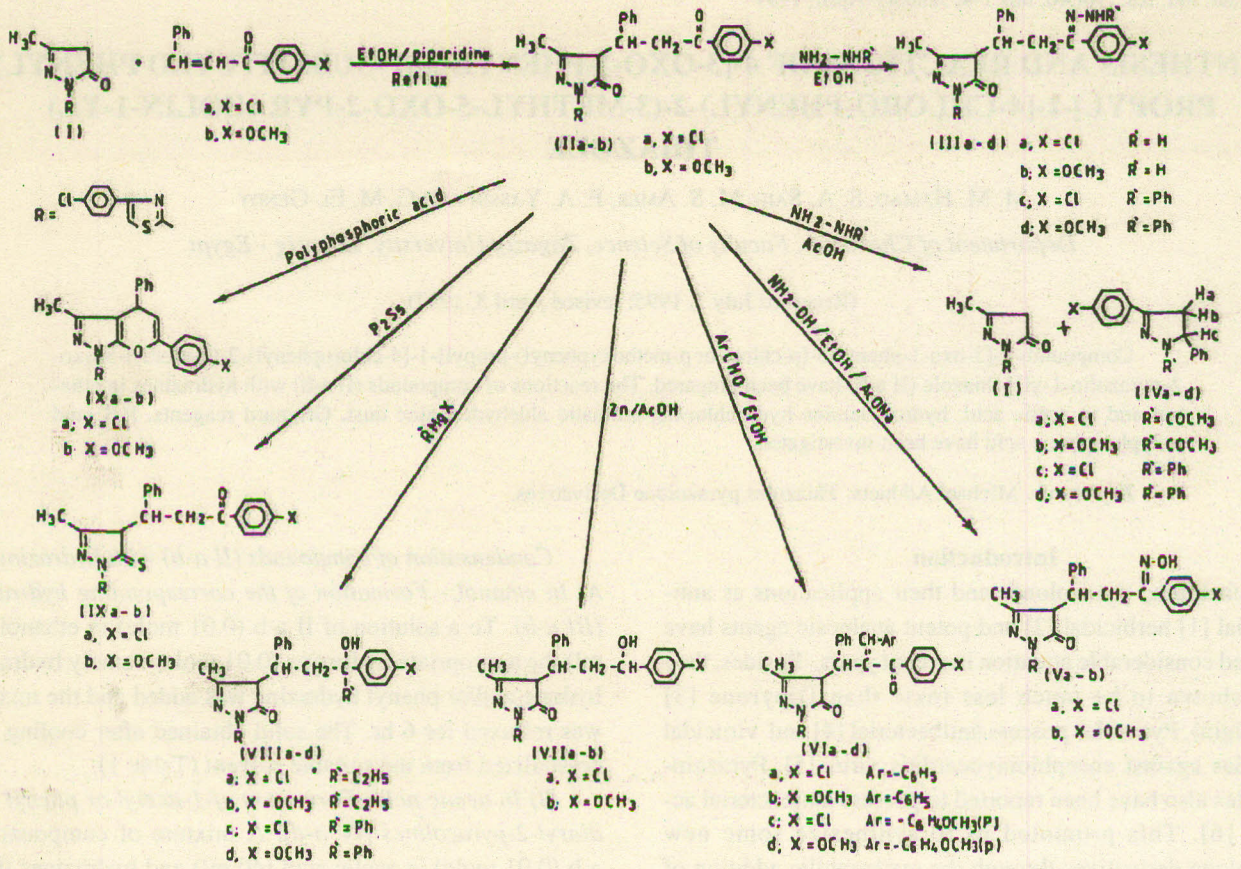
A) In ethanol:- Formation of the corresponding hydrazone (III a-b). To a solution of II a-b (0.01 mole) in ethanol (40 ml) the appropriate hydrazine (0.01 mole) namely hydrazine hydrate and/or phenyl hydrazine was added and the mixture was refluxed for 6 hr. The solid obtained after cooling was crystallized from the suitable solvent (Table 1).

B) In acetic acid: Formation of-1-acetyl or phenyl 3,5-diaryl-2-pyrazolines (IV a-d). A mixture of compounds II a-b (0.01 mole) in acetic acid (40 ml) and hydrazines (0.01 mole) namely hydrazine hydrate and/or phenyl hydrazine was heated under reflux for 6hr. The solid products obtained after cooling were crystallized from the proper solvent (Table 1).

- Condensation of compounds (II a-b) with hydroxylamine hydrochloride:- Formation of the corresponding oximes (V a-b). A mixture of II a-b (0.01 mole), hydroxylamine hydrochloride (0.01mole) and sodium acetate (3g) in ethanol (40ml.) was heated under reflux for 6 hrs. The product obtained after cooling was washed 3 times with water then recrystallized from the suitable solvent (Table I).

Condensation of compounds (II a-b) with aromatic aldehydes:-Formation of 4-(3-aryl-2-aroyl-1-phenyl-2-propenyl-1-(4'-p-chlorophenyl)-2'-(3-methyl-5-oxo-2-pyrazolin-1-yl) thiazole (VI a-d). A solution of IIa-b (0.01 mole) in ethanol (40ml), few drops of piperidine and aromatic aldehydes (0.01mole) namely benzaldehyde and/or anisaldehyde was heated under reflux for 6hr. The soild obtained after cooling was recrystallized from the suitable solvent (Table 1).

Reduction of compounds (II a-b) with zinc dust / acetic acid:- Formation of the corresponding secondary alcohols (VII a-b). A mixture of II a-b (0.01 mole) and zinc dust (5g) in acetic acid (40ml) was heated under reflux for 6hr. The unreacted zinc was filtered and the filtrate was concentrated.

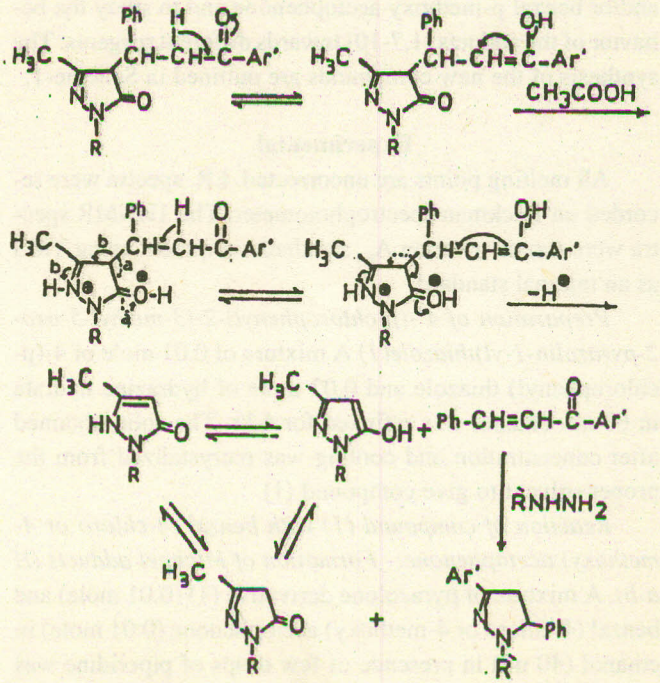


Scheme-1.

The solid product obtained after cooling was recrystallized from the suitable solvent (Table 1).

Action v of Grignard reagent on compounds (II a-b):- Formation of carbinol derivatives (VIII a-d). A solution of II a-b (0.01 mole) in dry toluene (40 ml) was treated with an ethereal solution of ethyl magnesium iodide and/or phenyl magnesium bromide (0.03 mole) in the course of 30 minutes. The reaction mixture was refluxed on steam bath for 1h, left overnight then poured slowly on saturated solution of ammonium chloride and extracted with ether. The ethereal layer was separated and dried on anhydrous sodium sulphate, filtered, evaporated and the oil obtained was solidified with light petrol (40-60) and recrystallized from the suitable solvent (Table 1).

Reaction of compounds (II a-b) with phophorous pentasulphide:-Formation of the corresponding thioxo-derivatives (IX a-b). A mixture of II a-b (0.01 mole) and phosphorous pentasulphide (0.01 mole) in dry xylene (35 ml) was heated under reflex for 6hr . The reaction mixture was filtered off while hot. The xylene layer was concentrated, cooled and the solid obtained after cooling was crystallized from the suitable solvent (Table 1).



Scheme-2.

TABLE 1. ANALYTICAL DATA OF COMPOUNDS (1-X).

Comp. No	M.P. °C	Yield % Solvent	Molecular Formula (Mol. wt.)	Elemental analysis calc./ Found C	H	N
I	270	74 (BuOH)	$C_{13}H_{10}N_3OSCl$ (291.8)	53.5 53.2	3.46 3.13	14.4 14.2
IIa	224	68 (Dioxane)	$C_{28}H_{21}N_3O_2SCl_2$ (534.5)	62.9 62.7	3.96 3.75	7.9 7.7
IIb	182	55 (Dioxane)	$C_{29}H_{24}N_3O_3SCl$ (530)	65.7 65.4	4.56 4.44	7.9 7.7
IIIa	191	64 (EtOH)	$C_{28}H_{23}N_5OSCl_2$ (548.5)	61.3 61.1	4.23 4.01	12.8 12.6
IIIb	163	59 (EtOH)	$C_{29}H_{26}N_5O_2SCl$ (544.1)	64.0 63.7	4.82 4.50	12.9 12.6
IIIc	293	53 (Benzene)	$C_{34}H_{27}N_5OSCl_2$ (624.6)	65.4 65.1	4.36 4.23	11.2 10.9
IIId	262	48 (Benzene)	$C_{35}H_{30}N_5O_2SCl$ (620.2)	67.8 67.6	4.88 4.65	11.3 11.1
IVa	247	68 (AcOH)	$C_{17}H_{15}N_2OCl$ (298.8)	68.3 68.1	5.06 4.84	9.4 9.2
IVb	215	57 (AcOH)	$C_{18}H_{18}N_2O_2$ (294.4)	73.5 73.3	6.16 6.04	9.5 9.2
IVc	231	61 (Pet. ether)	$C_{21}H_{17}N_2Cl$ (332.8)	75.8 75.5	5.15 4.93	8.4 8.2
IVd	217	48 (Pet. ether)	$C_{22}H_{20}N_2O$ (328.4)	80.5 80.3	6.14 6.01	8.5 8.3
Va	253	71 (EtOH)	$C_{28}H_{22}N_4O_2SCl_2$ (549.5)	61.2 60.9	4.04 3.93	10.2 10.0
Vb	231	63 (EtOH)	$C_{29}H_{25}N_4O_3SCl$ (545.1)	63.9 63.6	4.62 4.31	10.3 10.1
VIa	275	63 (EtOH)	$C_{35}H_{25}N_3O_2SCl_2$ (622.6)	67.5 67.2	4.05 3.83	6.7 6.5
VIb	242	54 (EtOH)	$C_{36}H_{28}N_3O_3SCl$ (618.1)	70.0 69.8	4.57 4.26	6.8 6.5
VIc	259	58 (EtOH)	$C_{36}H_{27}N_3O_3SCl_2$ (652.6)	66.3 66.1	4.17 4.05	6.3 6.1
VId	217	50 (EtOH)	$C_{37}H_{30}N_3O_4SCl$ (648.2)	68.6 68.4	4.67 4.44	6.5 6.2
VIIa	143	68 (AcOH)	$C_{28}H_{23}N_3O_2SCl_2$ (536.5)	62.7 62.5	4.32 4.01	7.8 7.6
VIIb	119	59 (AcOH)	$C_{29}H_{26}N_3O_3SCl$ (532.1)	65.5 65.2	4.93 4.82	7.9 7.6
VIIIa	186	54 (Pet. ether)	$C_{30}H_{27}N_3O_2SCl_2$ (564.5)	63.8 63.6	4.82 4.60	7.4 7.2
VIIIb	143	41 (Pet. ether)	$C_{31}H_{30}N_3O_3SCl$ (560.1)	66.5 66.2	5.40 5.11	7.5 7.2
VIIIc	253	43 (Pet. ether)	$C_{34}H_{27}N_3O_2SCl_2$ (612.6)	66.7 66.5	4.44 4.32	6.9 6.7
VIIId	211	39 (Pet. ether)	$C_{35}H_{30}N_3O_3SCl$ (608.2)	69.1 68.8	4.97 4.76	6.9 6.6
IXa	164	59 (xylene)	$C_{28}H_{21}N_3O_2S_2Cl$ (550.5)	61.1 60.9	3.85 3.52	7.6 7.3
Xb	122	53	$C_{29}H_{24}N_3O_2S_2Cl$ (546.1)	63.8 63.5	4.43 4.32	7.7 7.4
Xa	215	52 (Pet. ether)	$C_{28}H_{19}N_3OSCl_2$ (516.4)	65.1 64.9	3.71 3.50	8.1 7.8
Xb	164	43 (Pet/ ether)	$C_{29}H_{22}N_3O_2SCl$ (512)	68.0 67.7	4.33 4.01	8.2 8.0

(Cont'd...)

(Table 1 Cont'd...)

- Pet. ether b.p 60/80°C

Reaction of compounds (II a-b) with polyphosphoric acid: Formation of pyrazolopyran derivatives (X a-b). A mixture of II a-b (1.5 gm) and polyphosphoric acid (20 ml) was heated in an oil bath at 220°C with occasional shaking for 2hr. The contents were poured into crushed ice with stirring, extracted with ether and the ethereal solution was washed with aqueous solution of sodium hydroxide (5%) then with water, the ethereal solution was dried (anhydrous $MgSO_4$) then filtered and evaporated to give a solid which was crystallized from the suitable solvent (Table 1).

Results and Discussion

Thus, the reaction of benzal (4-chloro or 4-methoxy) acetophenone with compound (1) in boiling ethanol and in the presence of few drops of piperidine gave the Michael adducts 4-[3-oxo-1-phenyl-3-(p-chloro or p-methoxy phenyl) propyl]-1-4-(p-chlorophenyl]-2-(3-methyl-5-oxo-2-pyrazolin-1-yl) thiazole (II a-b). Condensation of compounds (II a-b) with hydrazine hydrate and/or phenyl hydrazine in boiling ethanol gave the corresponding hydrazones; 4 -[3-(p-chloro or p-methoxy phenyl)-1-phenyl propyl -3-hydrazone or phenyl hydrazone)]-1-[4-p-chlorophenyl-2-(3-methyl-5-oxo-2-pyrazolin-1-yl) thiazole (III a-b). However, condensation of (IIa-b) with hydrazine hydrate and/or phenyl hydrazine in boiling acetic acid yielded two products; one 4 (p-chlorophenyl)-2-(3-methyl-5-oxo-2-pyrazolin-1-yl) thiazole (1) as a minor product and 1-acetyl or phenyl-3- phenyl-5- (p-chloro or p-methoxy phenyl)-2-pyrazolines (IV a-d) major product. The latter was prepared authentically by treatment of the chalcones namely banzal p-chloro and/ or p-methoxy acetophenone with hydrazine hydrate and/or phenyl hydrazine in boiling acetetic acid. The mechanism of this reaction is illustrated in Scheme (2). On the other hand, condensation of compounds (II a-b) with hydroxylamine hydrochloride in boiling ethanol in the presence of sodium acetate gave the corresponding oximes 4-[3-(p-chloro or p-methoxy phenyl-1-phenyl-propyl oxime]-1-[4-(p-chlo-rophenyl)-2-(3-methyl-5-oxo-2-pyrazolin-1-yl] thiazole (V a-b).

Also, condensation of compound (II a-b) with aromatic aldehydes namely, benzaldehyde and/or anisaldehyde gave

TABLE 2. SPECTRAL DATA OF THE PREPARED COMPOUNDS (II-X).

Comp No.	Characteristic absorption IR Frequencies in cm^{-1} / ^{1}HNMR in δ values
IIa	IR: 1710 (C=0 of pyrazolone), 1680 (C=O) and 1610 (C=N)
IIb	^{1}HNMR:- 2.3 (s; 3H,-CH_3); 3.1 (m; 1H,-1CH ph); 3.3 (d; 1H, pyrazolone H); 3.5 (5; 3H, OCH_3) 4.2 (d; 2H,-CH_2CO) 7.1-8.1 (m; 14H, 13 arom H and 1H thiazole)
IIIa	IR:-3320-3220 (NH_2), 1700 (C=O of pyrazolone and 1615 (C=N)
IIIb	^{1}HNMR:- 2.2 (s; 3H, CH_3); 2.9 (m; 1H, -CHph); 3.1 (d; 1H, pyrazolone H); 3.4 (s; 3H, OCH_3); 3.7 (d; 2H, -CH_2CO) 6.4 (d; 2H, NH_2); 7.15-8.11 (m; 14H, 13 arom. H and 1H thiazole)
IIIc	IR:-3260 (NH), 1705 (C=O of pyrazolone) and 1605 (C=N)
IIId	^{1}HNMR:-2.2 (s; 3H, CH_3); 2.85 (m; 1H,- 1CHph) 3.13 (d; 1H, pyrazolone H); 3.26; (s, 3H OCH_3); 3.66 (d; 2H,-CH_2 CO); 6.97-7.85 (m; 19H, 18 arom.H and 1H thiazole)
IVa	IR:- 1670 (C=O) and 1615 (C=N)
	IR:- 1660 (C=O) and 1610 (C=N)
IVb	^{1}HNMR:- 2.51 (q; 1H, 1Ha); 3.1 (q; 1H, Hb); 3.54 (s; 3H, CH_3CO);
IVc	5.1 (q; 1H, Hc) and at 6.75-7.75 (m; 9H, Hb); arom H)
IVd	^{1}HNMR:- 2.76 (d; 2H, CH_2 CO); 3.27 (s; 3H, OCH_3) 3.58 (m; 1H-1CHph) and at 7.13-7.87 (m; 12H, arom, H)
Va	IR:- 3400 (OH), 1710 (C=O) and 1610 (C=N)
Vb	^{1}HNMR:- 2.22 (s; 3H, CH_3); 2.83 (m; 1H,-1CHph); 3.17 (d; 1H, pyrazolone H); 3.23 (s; 3H, OCH_3); 3.96 (d; 2H, 1CH_2C=N-OH); 6.65 (s; 1H, OH and 6.86-7.66 (m; 14H, 13 arom.H and 1H thiazole)
VIa	^{1}HNMR:- 2.22 (s; 3H, CH_3); 2.83 (m; 1H,-1CHph); 3.18 (d; 1H, pyrazolone H); 6.65 (s; 1H, C=CH-) and at 7.19-7.86 (m; 14H, 13 arom.H and 1H thiazole)
VIb	IR;- 1715 (C=O of pyrazolone), 1680 (C=O); 1630 (C=C) and 1615 (C=N)
VIIa	IR:- 3500-3400 (OH) 1705 (C=O, pyrazolone) and 1605 (C=N)
VIIIa	^{1}HNMR:- 1.13 (t; 3H, CH_2-CH_3); 1.91 (q; 2H, CH_2-CH_3) 2.16 (s; 3H, CH_3). 2.3 (d; 2H, CHph)-CH_2) 3.23 (m; 1H,-1CHph), 3.8 (d; 1H, pyrazolone H), 6.7 (s; 1H, OH), 7.11-7.87 (14H, 13 arom.H and 1H thiazole)
VIIIb	IR:- 3400 (OH) and 1705 (C=O) and1600 (C=N)
VIIIc	IR:- 3450 (OH), 1720 (C=O) and 1615 (C=N)
VIIId	1HNMR:- 2.17 (s; 3H, -CH_3), 2.45 (m; 1H, CHph), 3.5 (s; 3H, OCH_3) 3.82 (d; 1H, pyrazolone H) and 7.12-7.93 (m; 19H, 18H arom, and 1H thiazole)
IXa	^{1}HNMR:- 2.14 (s; 3H, CH_3), 2.45 (m; 1H, -CHph), 2.72 (d; 1H, pyrazolone H), 3.58 (d; 2H, -phCH-CH_2), 7.13-7.89 (m; 14H, 13H arom, and 1H thiazole)
IXb	IR:- 1690 (C=O) 1470 (C=N) and 1350 (C=S)
Xa	IR:- Disappearance bands which explain the presence of (C=O) groups and appearance bands near 1300 (C-O-C)

(Cont'd...)

(Table 2 Cont'd...)

the corresponding 4-[3-(phenyl or p-methoxy phenyl)]-2-(p-chloro or p-methoxybenzoyl-1-phenyl-2-propenyl)-1-(4-p-chlorophenyl)-2-(3-methyl-5-oxo-pyrazolin-1-yl) thiazoles (VI a-d). Reduction of compounds (II a-b) with zinc dust in boiling acetic acid gave the corresponding secondary alcohols 4-[3-hydroxy-1-phenyl-3-(p-chloro or p-methoxy phenyl propyl]-1-[4(-p-chlorophenyl)-2-(3-methyl-5-oxo-2-pyrazolin-1-yl) thiazole (VII a-b).

In the present, investigation, it was found that the treatment of compound (II a-b) with ethylmagnesium iodide and/ or phenyl magnesium bromide resulted in the formation of 4-[3-hydroxy-1-phenyl-3-ethyl or phenyl-3-(p-chloro or p-methoxy phenyl) propyl]-1-(4-p-chlorophenyl)-2-(3-methyl-5-oxo-2-pyrazolin-1-yl) thiazole (VIII a-d). Also, the reaction of compounds (II a-b) with phosphorous pentasulphide in boiling xylene gave 4-(3-oxo-1-phenyl-3-(p-chloro or p-methoxy phenyl) propyl-1-(4-p-chlorophenyl)-2-(3-methyl-5-oxo-2-pyrazolin-1-yl) thiazole (IX a-b). On the other hand, the reaction of compounds (II a-b) with polyphosphoric acid gave 1-[4(p-chlorophenyl) thiazolyl] -3-methyl-4-phenyl 6-(p-chloro or p-methoxyphenyl)- pyrazolo[3,4-b] -4H pyran (X a-b).

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