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Studies on Heterocyclic Nitrogen Compounds: Synthesis of Isolated Pyrazolines, Isoxazolines and Pyrimidines Derivatives

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Isolated pyrazoline, isoxazoline, pyrimidine and pyrimidine thione derivatives were synthesised through cycloaddition reaction on a newly synthesised α, β–unsaturated ketonic centre. The synthetic derivatives posses high activity against different species of bacteria and fungi.

INTRODUCTION

The heterocyclic nitrogen compounds, especially pyrazoline, isoxazoline and pyrimidine derivatives play a vital role in many biological processes and as a synthetic drugs[1–6], plant growth regulators[7], dyes[8] and corrosion inhibitors[9]. In one of our previous papers[10], we have investigated the α, β-unsaturated ketonic center isolated by a phenyl moiety attached to the 5–position in a pyrazoline nucleus through azomethine atom. In addition to our presentation in the chemistry of pyrazoline nucleus[11–14], we have investigated here the reactivity of α, β-unsaturated ketonic system build up on carbon –3– of 1–phenyl pyrazol –5– one.

RESULTS AND DISCUSSION

On acetylation of 3–amino –1–phenyl pyrazoline–5– one (1) using acetic anhydride afforded a quantitative yield of 3–acetylaminopyrazolone (2) which on condensation with some selected aromatic aldehydes results in formation of the α, β– unsaturated center (3a – f).

The structures of these chalcones were elucidated via elemental analysis, IR and ^{1}H–NMR spectra, which shows absorption at 4.5–6.8 ppm due to two ethylenic hydrogen proton. The reactivity of these chalcones (3a–f) prompted us to interact them with hydrazine hydrate, phenylhydrazine and hydroxylamine hydrochloride under various conditions[10], affording the corresponding 3–imino (N–acetyl-pyrazoline) –1–phenylpyrazol –5–one derivatives (4a–f); –3–imino (N–phenyl-pyrazoline)–1–phenylpyrazol–5–one derivatives (5a–f) and –3–imino (isoxazo-line)–1– phenylpyrazol –5–one derivatives (6a–f) respectively.

The chemical structures of these compounds were based upon elemental analysis; IR and ^{1}H-NMR spectra *e.g*, ^{1}H–NMR for compound (4a) shows a singlet at 1.3 for 3H, CH_3–CO–N; 2.2–2.4 for two $-CH_2$ and at 6.6 for –CH–, besides the multiplet at 6.9–8.4 for two aromatic mono substituted products. Whereas the IR spectra of the compound (4a) shows an absorption bands at 1670, 1740 and 3500–3300 cm^{-1} for acyl, the ring ketone and for the imino group respectively.

Also, the activation exerted by the carbonyl group on the exocyclic double bond in these chalcones render them available for addition of various amino compounds *e.g*, interaction with urea and thiourea afforded pyrimidine and thiopyrimidine derivatives (7,8a–f) respectively. The elemental analysis; IR and ^{1}H–NMR spectra were used to confirm the structure of these derivatives.

Biological Screeing of Some Selected Compounds

The selected compounds were dissolved in ethylene glycol. The bacteria and fungi used in these experiments were previously found to be succeptible to several soil micro organisms tested. Using filter paper disc method for biological screeing of bacteria and fungi, the results are reported in the following Table-1.

TABLE 1

Organism	1	2a	2b	3a	3b	3f	4a	5a	5b	5e	6a	7a
Bacterial Species												
B. Stearother mophilus 92–L.N.	H	L	H	M	N	L	N	N	M	N	L	L
B. Stearother Nmophilus 98–L.N.	M	N	N	L	M	N	N	N	L	L	N	N
Saricinalutea	H	M	L	H	N	L	N	N	N	M	L	N
E. Coli	L	L	M	M	L	N	N	N	L	L	N	L
Fungal Species												
Penicillium cyclopium	H	M	L	M	N	L	N	N	M	N	N	N
Asperigillus egyptiocus	M	L	N	N	L	L	N	N	L	L	M	N
Alternari	H	H	L	M	N	L	N	N	M	N	N	L

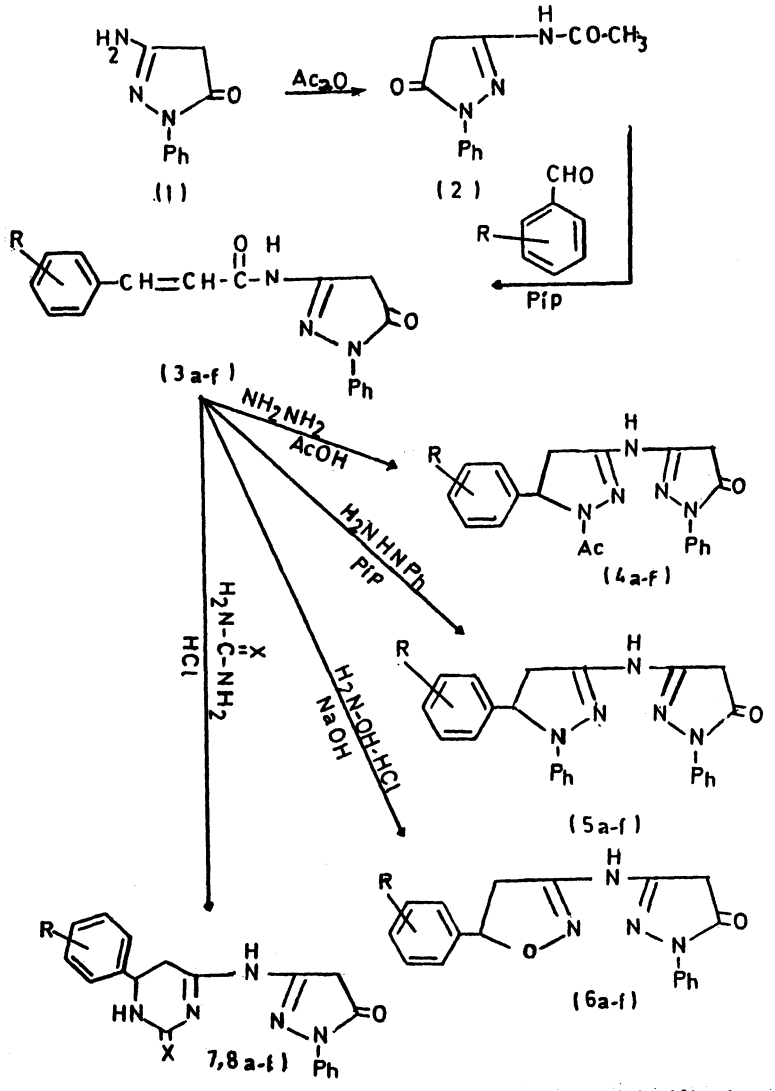
High potency: H; Medium potency: M; Low potency: L and No potency: N.

EXPERIMENTAL

Melting points are uncorrected. IR spectra (KBr) were recorded on a Unicom SP 200 spectrophotometer. The elemental analysis at Micro Analytical Center, Cairo University.

I Preparation of 3-acetylamino-1-phenylpyrazoline-5-one (2)

Pure amount of 3-amino-1-phenylpyrazolone (1) was fused under reflux in acetic anhydride for 4 hrs. The reaction mixture was then allowed to cool, the



precipitate was filtered off and crystallized from ethanol with activated charcoal to give red needles m.pt. 130°C, yield 80%.

II 3-Imino (α, β-unsaturated ketone)-1-phenylpyrazoline-5-one (3a-f):

A mixture of equimolar amounts of 3-acetylaminopyrazolone and the selected aromatic aldehydes were refluxed in ethanol and piperidine as a catalyst for 10–12 hrs. Concentrate the sulution, cool, then triturated with petroleum ether (40°–60°C) where the products were separated, washed with pet. ether, dried and crystallized from proper solvents as brownish crystales. The experimental data are given in the Table-2.

TABLE 2

Comp. No.	R	Mol. formula	M. pt °C	Yield %	Analysis % Calc. (Found)		
					C	H	N
3-Imino-(chalcones)-1-phenylpyrazolone Derivatives (3a–f)							
3a	H	$C_{18}H_{15}N_3O_2$	140	70	70.82 (70.70)	4.92 (4.89)	13.77 (13.80)
3b	*p*- NO_2	$C_{18}H_{14}N_4O_4$	180	90	61.71 (61.50)	4.00 (4.08)	16.00 (15.88)
3c	*o*-OH	$C_{18}H_{15}N_3O_3$	145	60	67.29 (67.18)	4.67 (4.48)	13.08 (13.09)
3d	*p*-OH	$C_{18}H_{15}N_3O_3$	160	65	67.29 (67.23)	4.67 (4.54)	13.00 (13.11)
3e	*p*-OCH_3	$C_{19}H_{17}N_3O_3$	200	70	68.06 (68.11)	5.07 (5.02)	14.33 (14.12)
3f	*p*-NMe_2	$C_{20}H_{20}N_4O_2$	190	75	68.97 (68.74)	5.75 (5.64)	16.09 (16.11)
3-Imino-(N-acetylpyrazoline) Derivatives (4a–f)							
4a	H	$C_{20}H_{19}N_5O_2$	250	60	66.48 (66.32)	5.26 (5.12)	19.39 (19.22)
4b	*p*-NO_2	$C_{20}H_{18}N_6O_4$	150	80	59.11 (59.08)	4.43 (4.32)	20.69 (20.53)
4c	*o*-OH	$C_{20}H_{19}N_5O_3$	165	40	63.66 (63.51)	5.04 (5.11)	18.57 (18.48)
4d	*p*-OH	$C_{20}H_{19}N_5O_3$	215	50	63.66 (63.54)	5.04 (5.09)	18.57 (18.49)
4e	*p*-OCH_3	$C_{21}H_{21}N_5O_3$	245	70	64.45 (64.32)	5.37 (5.21)	17.90 (17.89)
4f	*p*-NMe_2	$C_{22}H_{24}N_6O_2$	155	80	65.35 (65.25)	5.94 (5.87)	20.79 (20.61)
3-Imino-(N-phenylpyrazoline)-Derivatives (5a–f)							
5a	H	$C_{24}H_{21}N_5O$	265	65	72.91 (72.75)	5.32 (5.28)	17.72 (17.54)
5b	*p*-NO_2	$C_{24}H_{20}N_6O_3$	150	75	65.45 (65.41)	4.55 (4.34)	19.09 (19.15)
5c	*o*-OH	$C_{24}H_{21}N_5O_2$	235	65	70.07 (70.12)	5.11 (5.02)	17.03 (17.10)
5d	*p*-OH	$C_{24}H_{21}N_5O_2$	165	70	70.07 (70.14)	5.11 (4.89)	17.03 (17.11)
5e	*p*-OCH_3	$C_{25}H_{23}N_5O_2$	160	75	70.59 (70.43)	5.41 (5.36)	16.47 (16.32)
5f	*p*-NMe_2	$C_{26}H_{26}N_6O$	200	80	71.23 (71.13)	5.94 (5.87)	19.18 (19.08)

Comp. No.	R	Mol. formula	M. pt °C	Yield %	Analysis % Calc. (Found)		
					C	H	N
		3-Imino-(isoxazoline)-Derivatives (6a–f)					
6a	H	$C_{18}H_{16}N_4O_2$	145	40	67.92 (67.79)	4.40 (4.35)	17.61 (17.54)
6b	*p*-NO_2	$C_{18}H_{15}N_5O_4$	183	65	59.50 (59.34)	3.58 (3.45)	19.28 (19.19)
6c	*o*-OH	$C_{18}H_{16}N_4O_3$	300	55	64.67 (64.54)	4.19 (4.11)	16.77 (16.58)
6d	*p*-OH	$C_{18}H_{16}N_4O_3$	280	60	64.67 (64.61)	4.19 (4.09)	16.77 (16.63)
6e	*p*-OCH_3	$C_{19}H_{18}N_4O_3$	175	70	65.52 (65.41)	5.59 (4.40)	16.09 (16.16)
6f	*p*-NMe_2	$C_{20}H_{21}N_5O_2$	275	80	66.48 (66.34)	5.26 (5.12)	19.39 (19.21)
		3–imino–(pyrimidine–one)–Derivatives (7a–f)					
7a	H	$C_{19}H_{17}N_5O_2$	160	60	65.71 (65.58)	4.89 (4.64)	20.17 (20.11)
7b	*p*-NO_2	$C_{19}H_{16}N_6O_4$	185	80	58.16 (58.11)	4.08 (4.12)	21.43 (21.21)
7c	*o*-OH	$C_{19}H_{17}N_5O_3$	240	50	62.81 (62.67)	4.68 (4.48)	19.28 (19.19)
7d	*p*-OH	$C_{19}H_{17}N_5O_3$	180	64	62.81 (62.71)	4.68 (4.56)	19.28 (19.12)
7e	*p*-OCH_3	$C_{20}H_{19}N_5O_3$	300	85	63.66 (63.52)	5.04 (5.11)	18.57 (18.37)
7f	*p*-NMe_2	$C_1H_{22}N_6O_2$	220	90	64.62 (64.54)	5.64 (5.55)	21.54 (21.43)
		3–Imino– (pyrimidine–thione)–Derivatives (8a–f)					
8a	H	$C_{19}H_{17}N_5OS$	300	70	62.81 (62.67)	4.68 (4.51)	19.28 (19.11)
8b	*p*-NO_2	$C_{19}H_{16}N_6O_3S$	230	80	55.88 (55.68)	3.92 (3.81)	20.59 (20.42)
8c	*o*-OH	$C_{19}H_{17}N_5O_2S$	145	75	60.16 (60.12)	4.49 (4.34)	18.47 (18.29)
8d	*p*-OH	$C_{19}H_{17}N_5O_2S$	155	70	60.16 (60.07)	4.49 (4.31)	18.47 (18.32)
8e	*p*-OCH_3	$C_{20}H_{19}N_5O_2S$	235	80	61.07 (61.11)	4.83 (4.68)	17.81 (17.64)
8f	*p*-NMe_2	$C_{21}H_{19}N_6OS$	190	85	62.07 (62.15)	5.42 (5.36)	20.69 (20.58)

III 3- imino (N-acetylpyrazoline) -1-phenylpyrazol-5-one derivatives (4a-f)

To an ethanolic solution of chalcones (3a-f), hydrazine hydrate (50%) was added in presence of few drops of acetic acid as a catalyst, the reaction mixture was refluxed for 10-15 hrs., the solution was concentrated and cooled. Trituration with pet. ether give a solid products. Collected and crystallized from benzene as pale brownish crystals. The physical data are given in Table-2.

IV 3- imino (N-phenylpyrazoline)-1- phenylpyrazol -5- one derivatives (5a-f)

The piperidine was used as a catalyst in the reaction of phenyl hydrazine with the chalcones, and the same way to separate the reaction products was used as above (Table-2).

V 3-imino (isoxazoline)-1-phenylpyrazol -5-one (6a-f)

Interaction of hydroxylamine hydrochloride with the chalcones (3a-f) in presence of sodium hydroxide as a catalyst the above procedure for separation the isoxazoline derivatives was used. (Table-2)

VI 3-imino (pyrimidine)-1-phenylpyrazol-5-one derivatives (7a-f; 8a-f)

Equimolar amounts of ethanolic solution of the chalcones and urea and/or thiourea in presence of concentrated hydrochloric acid were refluxed for about 10-15 hrs. The reaction solution was allowed to cool, the precipitated products after nuteralization with 5 N NaOH was filtered off, washed with cold water and crystallized from ethanol (Table-2).

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