Asian Journal of Chemistry Vol. 19, No. 6 (2007), 4479-4482

Synthesis of Some Biologically Active 3-Methyl-4-(substituted phenylhydrazono)-2-pyrazolin-5-ones and 2-Isoxazolin-5-ones

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Diazotized substituted anilines were treated with ethyl aceto acetate to yield ethyl-2-(substituted phenyl) hydrazono-3-oxo butyrates (**I**). Reaction of **I** with various ammonia derivatives ($PhNHNH_2$, H_2NNH_2, $H_2NOH{\cdot}HCl$) furnished pyrazoline-5-ones, isoxazoline-5 ones. The synthesized compounds have been tested for their biological activity.

Key Words: Synthesis, Biologically active, Pyrazolin-5-ones, 2-Isoxazolin-5-ones.

INTRODUCTION

Pyrazolone and isoxazolone compounds are associated with broad spectrum biological activities[1-3]. Compounds having hydrazono group shows a wide range of biological activities and 3-methyl-4-hydrazono-2-pyrazolin-5-one exhibited potential antidiabetic activity in rats[4,5]. Considering the biological importance of hydrazono group in pyrazolin-5-ones, some new substituted phenylhydrazono derivatives of 2-pyrazolin-5-ones and 2-isoxzolin-5-ones have been prepared (**Scheme-I**).

EXPERIMENTAL

Melting points were determined by open capillary method and are uncorrected. IR Spectra (cm^{-1}) were recorded on Perkin Elmer spectrophotometer in KBr pellets. ^1H NMR spectra were recorded on Bruker-4000 MHz FT-NMR. Purity of compounds was checked by TLC on silica gel plates.

Ethyl-2-substituted phenyl hydrazono-3-oxo butyrate (Ia-k): Substituted aniline (0.01 mol) was dissolved in a mixture of conc. HCl (5 mL) and water (8 mL) and cooled to 0ºC in an ice bath. To it a cold aqueous solution of sodium nitrate (1 g) was added.

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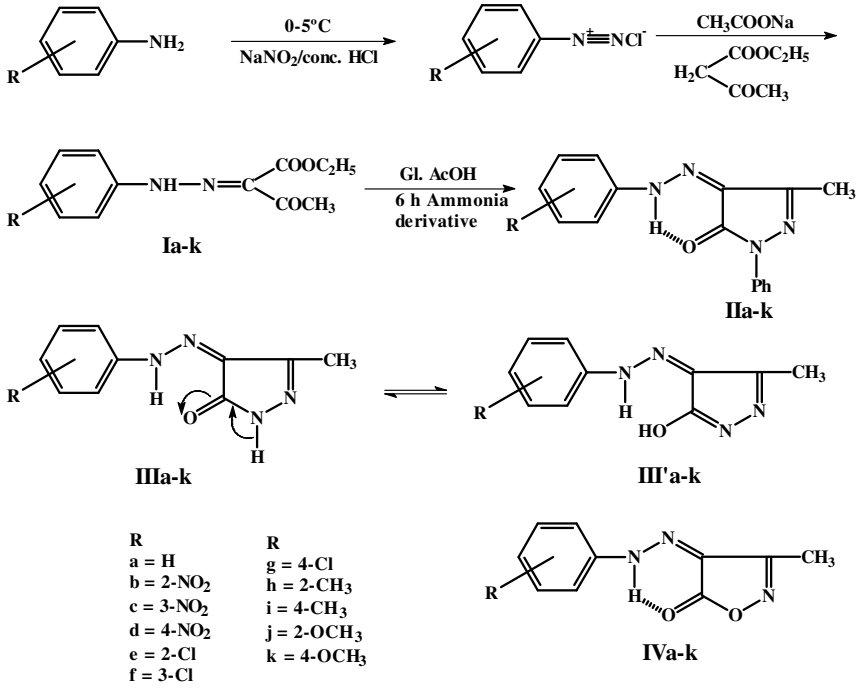

Scheme-I

The diazonium salt solution was filtered into a cooled solution of ethyl aceto acetate (0.01 mol) and sodium acetate (0.12 mol) in 25 mL of ethanol and the resulting yellow solid washed with water and then recrystallized from alcohol.

1-Phenyl-3-methyl-4-(substituted phenyl hydrazono)-2-pyrazolin-5-one (IIa-k): To **Ia-k** (0.001 mol) in glacial acetic acid (20 mL)was added and the mixture was heated on water bath for 6 h. Cooled and then allowed to stand over night. The resulting solid was dried and then recrystallized from acetic acid.

1-Hydro-3-methyl-4-(substituted phenyl hydrazono)-2-pyrazolin-5-one (IIIa-k): To **I a-k** (0.001 mol) dissolved in glacial acetic acid (20 mL) and hydrazine hydrate (0.001 mol) in glacial acetic acid was added and the mixture was heated on water bath for 6 h. Cooled and then allowed to stand over night. The resulting solid was dried and then recrystallized from acetic acid.

3-Methyl-4-(substituted phenyl hydrazono)-2-isoxazolin-5-one (IVa-k): To **Ia-k** (0.001 mol) dissolved in glacial acetic acid (20 mL) and hydoxyl aminehydrochloride (0.001 mol) in glacial acetic acid was added and the mixture was heated on water bath for 6 h. Cooled and then allowed to stand over night. The resulting solid was dried and then recrystallized from acetic acid.

RESULTS AND DISCUSSION

The m.p.s. and % yields of these compounds is recorded in Table-1. All the compounds were characterized by using IR, NMR and elemental analysis. The elemental analysis was found satisfactory. The spectral data are recorded in Table-2.

The IR band in the energy of 3600-3200 cm^{-1} for compounds **IIIa-k** only indicate the presence of tautomeric form **III'** where NH proton of 1-position. migrates to oxygen of >C=O group at position 5. Such IR bands was found absent in compounds **II** and **IV**, where such proton is absent.

TABLE-1
PHYSICAL DATA OF THE SYNTHESIZED COMPOUNDS

Compd. no.	R	Ammonia derivative	m.p. (ºC)	Yield (%)
IIa	H		160	47.98
IIb	2-NO_2		220	86.00
IIc	3-NO_2		190	63.65
IId	4-NO_2		190	76.33
IIe	2-Cl		185	83.00
IIf	3-Cl	$PhNHNH_2$	140	48.12
IIg	4-Cl		132	44.77
IIh	2-CH_3		190	87.75
IIi	4-CH_3		142	40.73
IIj	2-OCH_3		168	74.48
IIk	4-OCH_3		142	45.26
IIIa	H		203	30.50
IIIb	2-NO_2		220	86.00
IIIc	3-NO_2		262	59.10
IIId	4-NO_2		260	54.51
IIIe	2-Cl		210	49.69
IIIf	3-Cl	$H_2NNH_2 \cdot H_2O$	210	40.33
IIIg	4-Cl		212	34.76
IIIh	2-CH_3		223	74.62
IIIi	4-CH_3		187	44.69
IIIj	2-OCH_3		232	45.47
IIIk	4-OCH_3		198	39.96
IVa	H		180	77.27
IVb	2-NO_2		183	75.41
IVc	3-NO_2		210	67.08
IVd	4-NO_2		183	28.00
IVe	2-Cl		142	45.58
IVf	3-Cl	$H_2NOH \cdot HCl$	160	20.20
IVg	4-Cl		181	30.19
IVh	2-CH_3		163	45.97
IVi	4-CH_3		202	73.15
IVj	2-OCH_3		173	48.90
IVk	4-OCH_3		185	68.13

TABLE-2
SPECTRAL DATA OF COMPOUNDS **II**, **III** AND **IV**

Compd.	IR (KBr, cm^{-1})	^1H NMR ($CDCl_3$) δ ppm
II	1659 (>C = O), 1555 (NH-N=C) 3200 (N-H)	2.30 (S,3H, CH_3), 7.20-7.98 (m, 5H, Ar-H) 13.64 (S, 1H, N-H)
III	1667 O (C=O), 1555 (NH-N =C) 3207 (N-H) & 3600-3200 (-OH)	2.40 (S, 3H,CH_3) 7.20-7.50 (m, 5H, Ar-H) 12.57 (S, 1H, N-H)
IV	1714 (>C =O) 1556 (NH-N=C) 3208 (N-H)	2.30 (S, 3H,CH_3) 7.20-7.50 (m, 5H, Ar-H) 12.70 (S, 1H, N-H)

The spectral data indicate that these compounds exist in hydrazono form. The structure requires that the >C=O group in position 5 should be in conjunction with >C=N group. A strong band appears in region 1667-1559 cm^{-1}. The presence of low frequency band may be attributed to the conjugation of cyclic >C=O group at position 5 with >C=N group. The lower frequency of >C=O group may also be due to participation of >C=O group at position 5 in hydrogen bonding with N-H group.

Biological activity: All the parazole and oxazole derivatives were screened for *in vitro* antibacterial activity against *Escheriachia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginasa* using paper disc diffusion method at 1000 mg/mL conc. using DMF as solvent. The results are tabulated in Table-3.

TABLE-3
RESULTS OF BIOLOGICAL ACTIVITY

Strain	Compound number						
	IIe	**IIIe**	**IIf**	**IIg**	**IIIg**	**IVi**	**IIIj**
E. coli	+	+	+	+	+	+	-
S. aureus	-	+	+	-	-	-	-
P. aeruginosa	+	+	-	-	+	+	+

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(*Received*: 7 June 2006; *Accepted*: 21 April 2007) AJC-5582