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Synthesis and antibacterial evaluation of substituted 3-methyl-2-pyrazolin-5-ones

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ABSTRACT

Nitrogen containing heterocycles are frequently found in privileged pharmacophores. Pyrazolin-5-ones are important nitrogen-containing five-membered heterocyclic compounds and have been found to be associated with a broad spectrum of bioactivities. The present work is directed towards the synthesis of some substituted-3-methyl-2-pyrazolin-5-ones. The synthesis of title compounds was achieved by the reaction of substituted ²-keto ester with substituted thiosemicarbazides and the synthesized compounds were screened for their antibacterial activity.

Keywords: Ethyl-2-substituted phenyl hydrazono-oxobutyrate, Substituted thiosemicarbazides, Pyrazolin-5-one, Antibacterial activity

INTRODUCTION

Pyrazolone moiety (a five-membered lactam ring containing two nitrogens and ketone in the same molecule or alternatively a derivative of pyrazole possessing an additional carbonyl/hydroxy group) has been the focus of medicinal chemists for over last 100 years because of the outstanding pharmacological properties shown by several of its derivatives[1,2] e.g. ampyrone, metamizole etc. The pyrazolone ring is the basis of agents with various biological activities including antihyperglycemic properties[1], anti-tumor necrosis factor activity[3-4], non-steroidal anti-inflammatory drugs (NSAIDs)[5], inhibition of human telomerase[6] and antibacterial activity[7]. Also, substituted 2-pyrazolin-5-ones play an important role as substructures of numerous pharmaceuticals, agrochemicals, dyes, pigments, as well as chelating agents and thus attract remarkable attention[8-10]. The mentioned properties prompted us to synthesize substituted-3-methyl-2-pyrazolin-5-ones.

EXPERIMENTAL

Material

All chemicals used in the synthesis were of analytical grade. Melting points were determined in open capillary tubes and are uncorrected. The purities of the compounds were checked on silica-gel-coated Al plates (Merck). IR spectra were recorded in KBr on a Perkin Elmer Spectrum RX-1 FT-IR spectrophotometer. ^{1}H-NMR spectra was measured on Advance Bruker DRX-300. Elemental analysis was performed on Elementor Vario EL III.

Synthesis of Ethyl-2-substituted phenyl hydrazono-oxobutyrate(1a-c)[11]

Substituted aniline (o-chloro, p-chloro and p-nitro)(0.01mole) was dissolved in a mixture of concentrated HCl (8 ml) and water (6 ml) and cooled to 0°C in an ice bath. To it a cold aqueous solution of sodium nitrate (0.03 mole) was added. The

Table 1: Physical and analytical data of compounds

S. No.	R	R'	Molecular Formula	Color	m.p. (°C)	Yield (%)	% N Found (Calc.)	% S Found (Calc.)
1.	2-Cl	4-CH_3	$C_{18}H_{16}ON_5SCl$	Orange	195	80.31	18.18 (18.15)	8.41 (8.30)
2.	2-Cl	2-OCH_3	$C_{18}H_{16}O_2N_5SCl$	Yellow	166	62.32	17.49 (17.41)	8.07 (7.96)
3.	2-Cl	4-OCH_3	$C_{18}H_{16}O_2N_5SCl$	Orange	178	64.80	17.45 (17.41)	8.05 (7.96)
4.	2-Cl	3,4-di CH_3	$C_{19}H_{18}ON_5SCl$	Orange	165	60.00	17.56 (17.52)	8.12 (8.00)
5.	2-Cl	2-Cl	$C_{17}H_{13}ON_5SCl_2$	Yellow	170	56.43	17.27 (17.24)	7.94 (7.88)
6.	4-Cl	4-CH_3	$C_{18}H_{16}ON_5SCl$	Orange	170	73.03	18.21 (18.15)	8.38 (8.30)
7.	4-Cl	2-OCH_3	$C_{18}H_{16}O_2N_5SCl$	Orange	165	70.35	17.51 (17.41)	8.03 (7.96)
8.	4-Cl	4-OCH_3	$C_{18}H_{16}O_2N_5SCl$	Orange	164	68.36	17.49 (17.41)	8.00 (7.96)
9.	4-Cl	3,4-di CH_3	$C_{19}H_{18}ON_5SCl$	Yellow	169	65.79	17.61 (17.52)	8.08 (8.00)
10.	4-Cl	2-Cl	$C_{17}H_{13}ON_5SCl_2$	Orange	155	61.83	17.30 (17.24)	7.92 (7.88)
11.	4-NO_2	4-CH_3	$C_{18}H_{16}O_3N_6S$	Orangish Yellow	191	72.33	21.30 (21.21)	8.14 (8.08)
12.	4-NO_2	2-OCH_3	$C_{18}H_{16}O_4N_6S$	DarkYellow	194	53.29	20.37 (20.31)	7.72 (7.76)
13.	4-NO_2	4-OCH_3	$C_{18}H_{16}O_4N_6S$	Orange	168	50.36	20.39 (20.31)	7.73 (7.76)
14.	4-NO_2	3,4-di CH_3	$C_{19}H_{18}O_3N_6S$	Brick Red	170	71.04	20.47 (20.42)	7.85 (7.80)
15.	4-NO_2	2-Cl	$C_{17}H_{13}O_3N_6SCl$	Golden Yellow	190	61.83	20.13 (20.16)	7.63 (7.68)

Table 2: Characterization data of compounds

Compound No.	IR (ν in cm^{-1})	^1H NMR (δ in ppm)
1	1110 (C=S), 1571 (-N=C-, pyrazolone ring), 1674 (>C=O)	1.22 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.38 (s, 1H, pyrazolone ring), 4.60 (s, 1H, NH), 6.35-7.86 (m, 8H, Ar-H).
6	1108 (C=S), 1574 (-N=C-, pyrazolone ring), 1673 (>C=O)	1.25 (s, 3H, CH_3), 2.35 (s, 3H, CH_3) , 3.36 (s, 1H, pyrazolone ring), 4.65 (s, 1H, NH), 6.42-7.70 (m, 8H, Ar-H)
11	1115 (C=S), 1560 (-N=C-, pyrazolone ring), 1686 (>C=O)	1.30 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.40 (s, 1H, pyrazolone ring), 4.73 (s, 1H, NH), 6.55-8.65 (m, 8H, Ar-H),

Table 3: Antibacterial activity of the compounds I-XII

Compound No.	E. coli	S. aureus
1	++	R
2	+	+
3	+	R
4	+ +	+ +
5	+	R
6	++	+ +
7	+	R
8	+	R
9	+ +	+
10	+ +	R
11	+	+
12	+	R
13	++	+
14	++	++
15	+	R
Streptomycin	+ + +	+ + +

Key to symbols: Resistance = R; slightly active = + (inhibition zone 6-9mm); moderately active = + + (inhibition zone 9-12 mm); highly active = + + + (inhibition zone> 12 mm).

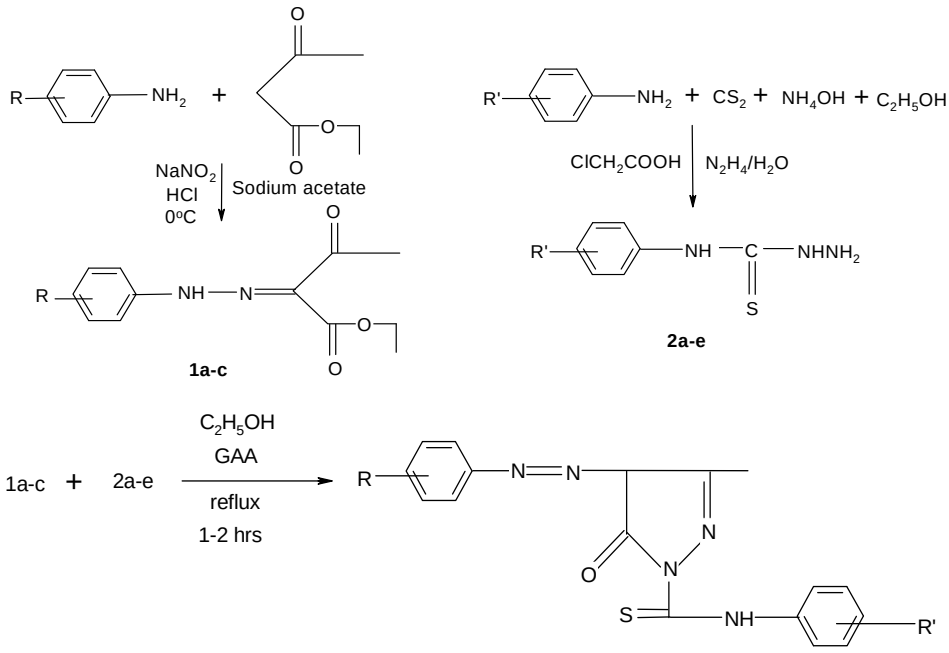
diazonium salt solution was added dropwise into a cooled solution of ethylacetoacetate (0.01 mole) and sodium acetate (0.12 mole) in ethanol (50 ml). The resulting solid was washed with water and recrystallized with absolute ethanol.

Synthesis of substituted thiosemicarbazides (2a-e)[12]

To a solution of substituted aniline (p-methyl, o-methoxy, p-methoxy, 3,4-dimethyl and o-chloro) (0.01mole) in ammonia (20ml) and water (5ml), CS_2 (7.5 ml) and ethanol (20ml) was added and stirred vigorously for 1 hour. Solution of Sodium carbonate(5.3 gm) and mono chloro acetic acid (9.5gm) in water (40ml) was added followed by hydrazine hydrate (6ml) and refluxed for 30-45 mins on steam bath. The resulting solid obtained on cooling was recrystallized with absolute ethanol.

General method for synthesis of substituted-3-methyl-2-pyrazolin-5-one (1-15)

To 1a-e (0.01 mole), ethanol (20ml) and 2a-e (0.01 mole) was added and refluxed for 1-2 hrs in presence of 2-4 drops of glacial acetic acid. The resulting solid obtained was cooled, filtered and was recrystallized with hot absolute ethanol.



4-(R) phenyl hydrazono-N'-(R')-phenyl thiocarbamoyl-3-methyl-2-pyrazolin-5-one

Compound No. 1-15

Antibacterial screenings

Filter paper disc technique using Hi-Media agar medium is employed to study the antibacterial activity of **1-15** against Staphylococcus aureus and Escherichia coli. The concentration of test compounds is 1,000 µg/ml. After 48 hr incubation at 37°C, zone of inhibition produced by each compound is measured in mm as shown in Table 3. Streptomycin is used as the reference drug and Dimethyl formamide as a control.

All tested compounds showed slight to moderate antibacterial activity.

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