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Research Article

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Synthesis and biological activity of 4”-substituted-2-(4'-formyl-3'-phenylpyrazole)-4-phenyl thiazole

Ramesh Chand Yadav, Pramod Kumar Sharma and Jaspal Singh

Nanak Chand Anglo Sanskrit College, Meerut, Uttar Pradesh, India

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ABSTRACT

4”substituted-2-(4'-formyl-3'-phenylpyrazole) 4-phenyl thiazole is synthesized by the condensation between acetophenone and 4-phenyl-2-hydrozino thiazole in presence of ethanol and glacial acetic acid using vilsmeier-haack reaction, which lead to the isolation of pyrazoline (Acetophenone hydrazone) as an intermediate. The structures of the synthesized compounds were confirmed by IR (Infra-Red Spectroscopy), 1H-NMR (Proton- Nuclear Magnetic Resonance Spectroscopy) and Mass spectral technique. The synthesized compounds were screened for their antifungal and antibacterial activities.

Key words: Antibacterial activity, vilsmeier-haack, pyrazoline, IR, 1H-NMR

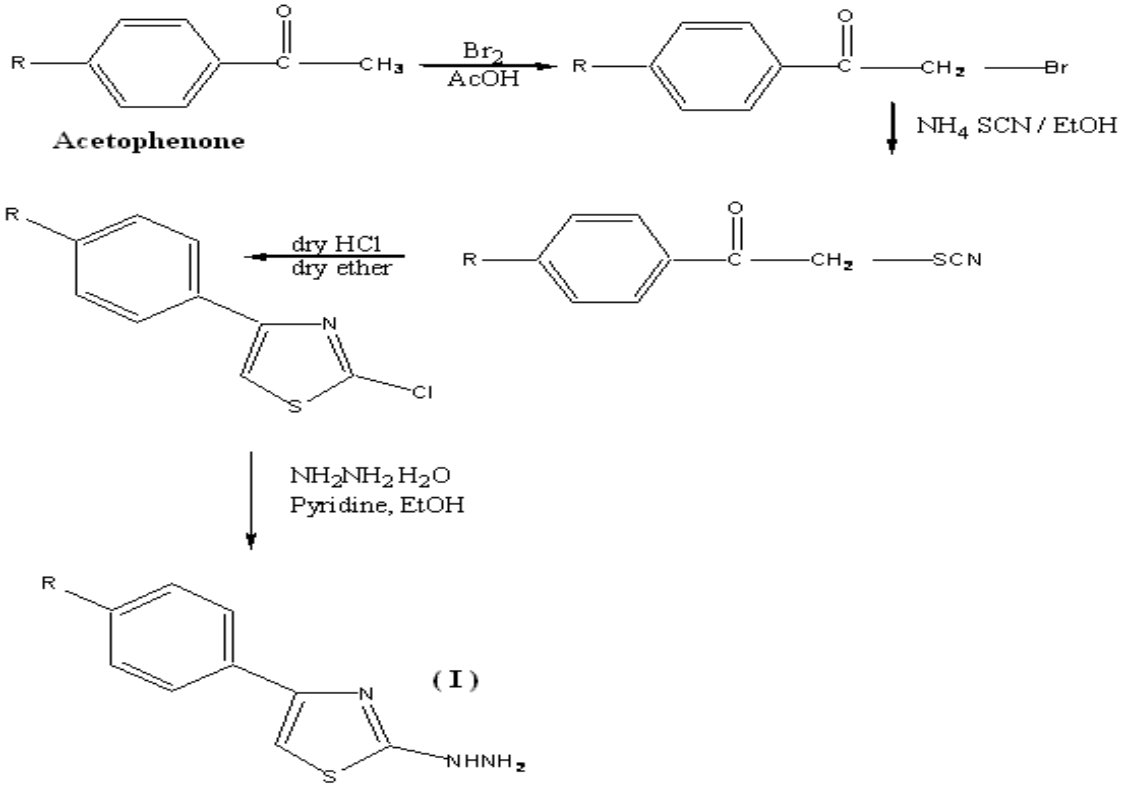
INTRODUCTION

Pyrazoles and their derivatives are important on account of use in therapy in different diseases [1-10] Antibacterial[11-15], fungicidal [16-21], antidiuretic[22-23], anticancer[24-29] and anti-HIV [30-31] antitumour [32], antianalgesic-inflamatory [33-37], anticonvulsant [38-39] properties. Pyrazole and its derivatives normally do not occur in nature probably due to difficulty in constructing a N – N bond by living organism, the notable exceptions being 3-n-nonyllpyrazole [40] isolated from Hottuynia Cordate, α-amino-β-1-pyrazolylpropionic acid[41] isolated from water-melon seeds and the alkoloid Withasominie-[42] i.e., 4-phenyl-1, 5-trimethyenepyrazole (3) isolated from Withania Somnifera. The method for the synthesis of 2-(4'-formyl-3'-phenylpyrazole) 4-phenyl thiazole involving the condensation between acetophenone and 4-phenyl-2-hydrozino thiazole, which lead to the isolation of intermediate pyrazoline (Acetophenone hydrazone) in the presence of ethanol and glacial acetic acid. In continuation of our interest on the sysnthesis of novel hetrocyclic system during the present investigation we used vilsmeier-haack reaction on above intermediate pyrazoline, and gives few 2-(4'formyl-3'phenylpyrazole-1-yl) 4-phenylthiazole.

EXPERIMENTAL SECTION

All the chemicals were used for synthesis are of analytical reagent grade. Melting points were taken in open capillaries in paraffin-oil-bath or an electronic apparatus are corrected. The Infrared (IR) spectra were scanned on KBr pellets or nujol mulls on perkin-Elmer 842 IR spectrophotometer and Perkin Elmer 1430 grating spectrophotometer. The proton Magnetic resonance ('H-NMR) spectra were recorded on Solution in CDCl3 and CDCl3-DMSO.d6 on a Multinuclear Brucker 300 AC. FT-NMR. Purity of the compounds was checked by TLC.TLC plates were coated with silicagel suspended in Chloroform-methanol mixture (1:1) and iodine vapours were used as the visualizing agent.

Synthesis of p-substitued-4-phenyl-2-hydrozino thiazole (I): p-substituted-4-phenyl -2-hydrozino thiazole needed for the present study have been synthesized from 4-substituted-acetophenones. A solution of an appropriate acetophenone (0.1 mol) in glacial acetic acid (75 ml) was placed in a conical flask. Bromine (16.0g, 0.1 mol) in glacial acetic acid (50ml) was added very slowly from the dropping funnel with constant stirring, keeping the temperature below 20^0. The 4-phenyl-2-hydrozino thiazole (I) were separated on pouring the reaction mixture on ice. The crude products were filtered at the pump, washed with cold ethanol and crystallized from ethanol. The reactions of the synthesis of compound I are as shown in scheme 1.



Scheme 1: Synthesis of p-substituted 4 Phenyl -2-hydrozinethiazole (I)
Where "R" may be -H (Ia), -CH3 (Ib), -OCH3 (Ic) or –Cl (Id)

The physical properties of p-substituted-4-phenyl-2-hydrozino thiazole (I) thus prepared are listed in Table 1.

Table 1: Physical properties of p-substituted 4-phenyl-2-hydrozino thiazole (I)

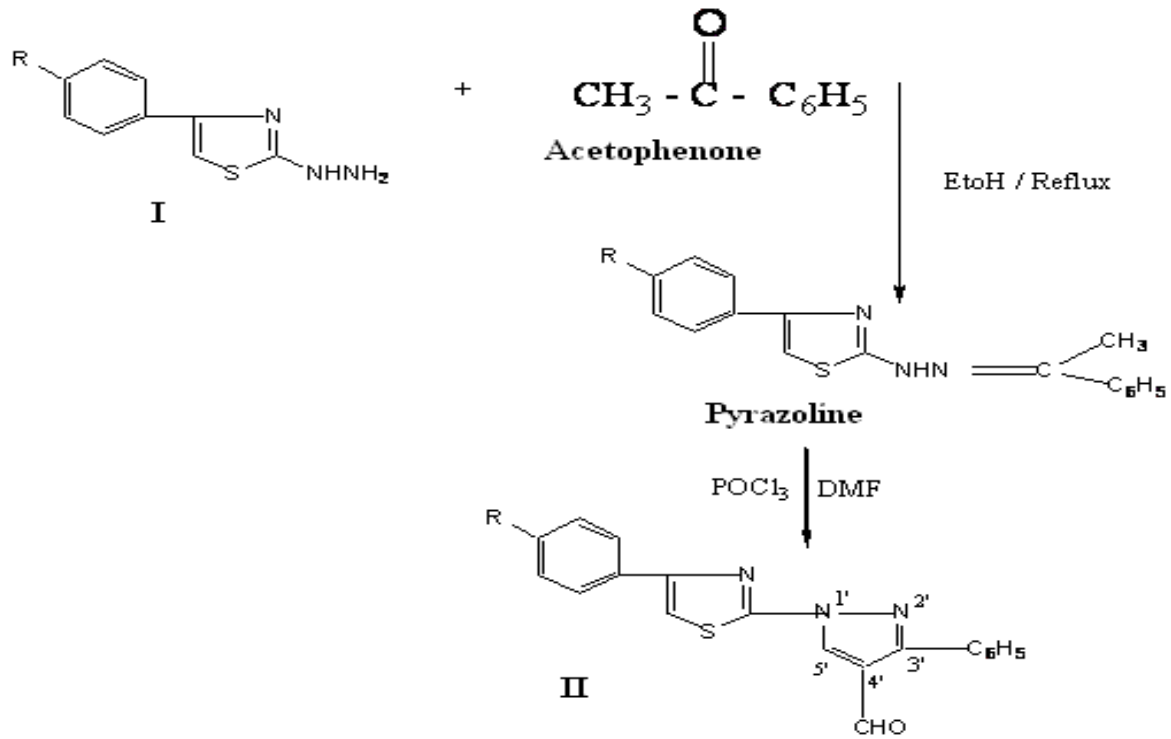
S.No.	R	Compound name	m.p. ^{0}C	Yield (%)
1	H	Ia	48-49	65
2	CH_3	Ib	50	62
3	OCH_3	Ic	70-71	57
4	Cl	Id	100	80

Synthesis of 2-(4'-formyl-3'-phenylpyrazole) 4-phenyl thiazole (IIa) : 2-(4'-formyl-3'-phenylpyrazole) 4-phenyl thiazole (IIa) was prepared by mixing 2-hydrazino-4-phenylthiazole (Ia) and acetophenone in ethanol was refluxed in the presence of a drop of acetic acid for 30 minutes. This forms the corresponding intermediate acetophenone-hydrazone (pyrazoline) in 80% yield and having m.p. 183^0. The hydrazone (pyrazoline) was treated with DMF-$POCl_3$ mixture at 80-85^{0}C for 5 hrs. The usual work up to the reaction mixture followed by crystallization from ethanol gave 4"-substituted-2-(4'-formal-3'phenylpyrazole-1'-yl) 4-phenylthiazole (IIa) as light yellow crystals, m.p. 116^0, yield 70%. The possible reactions for the synthesis of the compound II are shown in scheme 2.

Synthesis of 4"methyl-2-(4'-formyl-3'-phenylpyrazole) 4-phenyl thiazole (IIb): 4-methyl-2-hydrazino-4-phenylthiazole (Ib) and acetophenone in ethanol was refluxed in the presence of a drop of acetic acid for 30 minutes, the corresponding intermediate acetophenone-hydrazone (pyrazoline) was isolated in 80% yield. Thereafter Vilsmeier-Haack reaction on this intermediate with DMF-$POCl_3$ mixture at 80-85^{0}C for 5 hrs followed by usual work up of the reaction mixture results in the formation of 4"-methyl {2-(4-formyl-3'-pneylpyrazole)-1'-yl}-4-phenylthiazole (IIb) in 73% yield.

Synthesis of 4"methoxy-2-(4'-formyl-3'-phenylpyrazole) 4-phenyl thiazole (IIc): The synthesis of 4"-methoxy-{2-(4'formyl-3'-phenylpyrazol)-1'-yl}-4-phenylthiazole (IIc) was achieved by condensation of acctophenone with 4-methoxy-4'-phenylthiazole-2-yl-hydrozone (Ic) in the presence of a drop of acetic acid. The reaction first form corresponding intermediate hydrazone (pyrazoline) having m.p. 183^0 with a yield of 80%. This intermediate hydrazone was then subjected to Vilsmeier-Haack reaction into a mixture of DMF-$POCl_3$ at 80-85^0 for 5 hrs. The usual work up of the reaction mixture followed by crystallization for the crude product from ethanol provided 4"-methoxy-{2-(4'-formyl-3'-phenylpyrazol)-1'-yl}4-phenyl-thiazole (134c) as yellow crystals, m.p. 183^{0}C, yield 74%.

Synthesis of 4"-chloro-{2-(4'-formyl-3'-phenylpyrazol)-1'-yl} 4'-phenylthiazole (IId): the condensation of acctophenone with 4-chloro-4'-phenylthiazole-2-yl-hydrozone (Id) in the presence of a drop of acetic acid results into 4"-chloro-{2-(4'-formyl-3'-phenylpyrazol)-1'-yl} 4'-phenylthiazole (IId). The reaction first form corresponding intermediate hydrazone (pyrazoline) having m.p. 183^0 with a yield of 80%. This intermediate hydrazone was then subjected to Vilsmeier-Haack reaction into a mixture of DMF-$POCl_3$ at 80-85^0 for 5 hrs. Usual work up of the reaction mixture provided the corresponding pyrazole, i.e., 4"-chloro-{2-(4'-formyl-3'-phenylpyrazol)-1'-yl} 4'-phenylthiazole (IId) as light yellow needles, m.p. 185^0, yield 78%.



Scheme 2: Synthesis of 4"substituted-2-(4'-formyl-3'-phenylpyrazole) 4-phenyl thiazole (II)
Where "R" is = H (for compound IIa), -CH3 (for compound IIb), -OCH3 (for IIc) or –Cl (for IId)

BIOLOGICAL ACTIVITIES

Anti-bacterial activity:

Newly synthesized compounds (*IIa-d*) have been tested for their anti-bacterial activity against gram negative bacteria *Salmonella typhi* and *Pseudomonas aeroginosa* by agar plate disc diffusion method. Standard solution 1% to 6% of the 4''-substituted (2-4'formyl-3-phenlyl-pyrazole-1-yl) 4-phenylthiazole were prepared in methanol and water 50-50.

Anti-fungal activity*:*

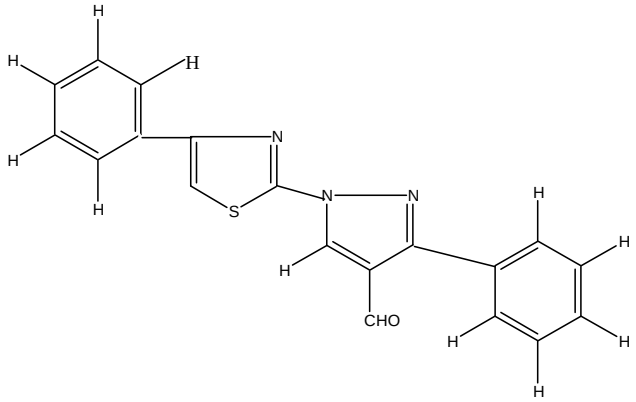
The same compounds were tested for their anti-fungal activity against *candida albican and aspergillus niger*.

RESULTS AND DISSCUSION

The IR and 1H-NMR examination of the compound 4''-substituted{2-(4'formyl-3'-phenylpyrazole)-1'-yl)-4-phenylthiazole show following results:

1. 2-(4'-formyl-3'-phenylpyrazole-1'-yl)-4-phenylthiazole (Ia): The compound shows following results by IR and 1H-NMR.

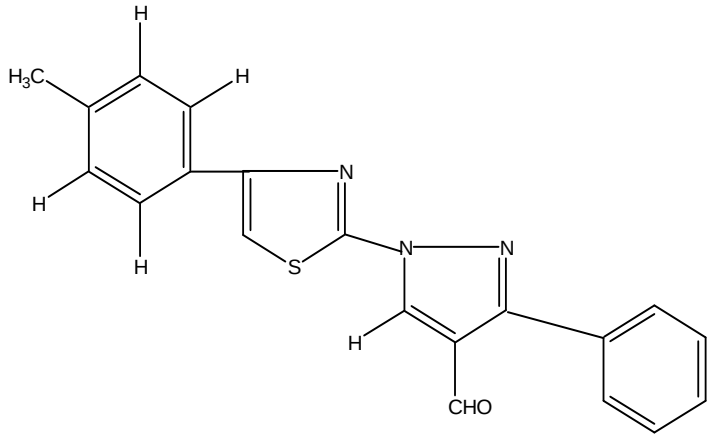
IR (Nujol, Vmax cm-1)	:	2820 (aldehydic C-H stretch) 1640 (δ,β-unsaturated C=O stretch)
'H NMR ($CDCl_3$)	:	δ 7.3-7.6 (m, 5H, arylproton) 7.6 – 7.85 (m, 4H, C_4-H, C_5-H,C_6-H) 9.0 (s, 1H, C_5'H) 10.0 (s,1H, C_4.-4 formylproton)



(II a)

4''-methyl{2-(4'formyl-3'-phenylpyrazole)-1'-yl)-4-phenylthiazole (IIb):

IR (ujol, Vmax Cm^{-1})	:	2820 (aldehydic C-H strecth) 1640 (α,β-unsaturated C = O stretch)
'H NMR ($CDCl_3$)	:	δ 2.32 (s, 1H, C_4-CH_3) 7.15 (dd, 1H, C_5-H, J = 8.0 and 2.5 Hz) 7.30-7.50 (m,5H, arylprotons) 7.55 (d, 1H, C_6-H, J = 2.5 Hz) 7.6-7.7 (d, 1H, C_2H, C_3-H, J = 8.0 Hz) 9.0 (s, 1H, C_5-H) 9.90 (s, 1H, C_4;-formylproton)

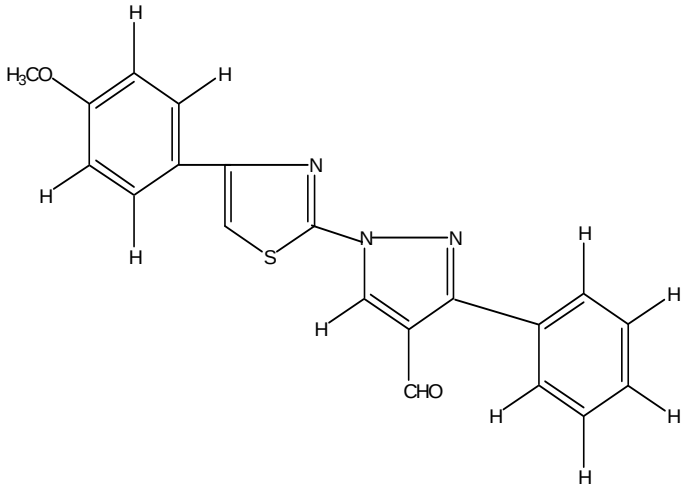


(IIb)

4"methoxy-{2-(4'-formyl-3'-phenylpyrazol)-1'-yl)4-phenylthiazole (IIc)

IR (ujol, Vmax Cm^{-1}) : 2810 (aldehydic C-H strecth)
1640 (α,β-unsaturated C = O stretch)

'H NMR ($CDCl_3$) : δ 3.70 (s, 3H, C_4-OCH_3)
6.95-7.05 (dd, 1H, C_5-H, J = 8.0 and 2.5 Hz)
7.2 (d, 1H, C_6-H, J = 2.5 Hz)
7.3-7.50 (m,5H, arylprotons)
7.6-7.8 (d, 1H, C_2-H, C_3-H, J = 8.0 Hz and 2.5 Hz)
8.85 (s, 1H, $C_{5'}$-H)
9.95 (s, 1H, C_4-formylproton)



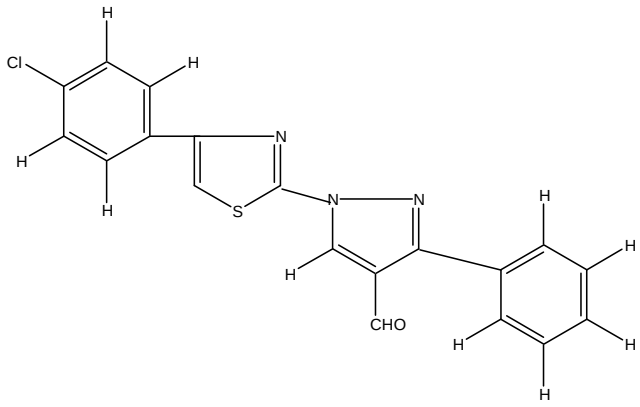
(IIc)

4"-Chloro-{2-(4'-formyl-3'-phenylpyrazol)-1'-yl}4-phenylthiazole (IId)

IR (nujol, Vmax Cm^{-1}) : 2850 (aldehydic C-H stretch)
1680 (α,β-unsaturated C = O stretch)

'H NMR ($CDCl_3$) : δ 7.45-7.54 (m, 5H, arylprotons)
7.83-7.87 (m, 3H, C_2-H, C_5-H, C_6-H)
9.02 (s, 1H, $C_{5'}$-H)
10.08 (s, 1H, C_4'-formylproton)

(II d)



Biological Activities:

It was observed that with the increase of concentration of compound the growth of all pathogens was affected. The standard solution with 2% of compound slightly reduced the growth while 5% compound solution was much effective in bring the count of micro-organism to all most nil. While solution with 6% of compound had all most same antimicrobial effect as of 5%. So, the compound 4''-substituted (2-4'formyl-3-phenlyl-pyrazole-1-yl) 4-phenylthiazole (IIa, IIb, IIc and IId) are biologically active.

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