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Synthesis and Biological Activity of 2-(3-Carboxy phenyl)-5-(4-substituted phenyl)-1-acetyl-2-pyrazolines

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3-Aminoacetophenone was diazotized and reacted with sodium cyanide to yield 3-cyano acetophenone (**1**). 3-Cyano acetophenone was treated with conc. sulphuric acid to obtain 3-carboxy acetophenone (**2**) which on condensation with various aromatic aldehydes in hydrotopes afforded substituted chalcones (**3a-e**). The chalcones (**3a-e**) on cyclization with hydrazine hydrate in glacial acetic acid furnished 2-(3-carboxy phenyl)-5-(4-substituted phenyl)-1-acetyl-2-pyrazolines (**4a-e**). The constitution of the products was supported by IR, NMR, Mass spectral data and elemental analysis. All the compounds synthesized have been screened for their biological activity.

Key Words: Synthesis, Pyrazolines, Antibacterial, Antifungal activity.

INTRODUCTION

Various substituted 2-pyrazolines have been associated with diverse pharmacological activity such as analgesic[1], antibacterial[2], antifungal[3], antidiabetic[4] and antitubercular[5]. The chalcone have been used as an intermediate in the synthesis of pyrazoline. Conventionally the chalcone preparation is carried out in solvents such as methanol, dimethyl formamide and alcohol. These solvents add burden on environment and on the health of humans. A literature survey reveals that the chalcone formation could be carried out in hydrotopic medium. In continuation of our work on the synthesis of biological active nitrogen heterocycles, it is worthwhile to synthesize a few novel pyrazoline derivatives (**4a-e**) and study them for their antibacterial and antifungal activities.

EXPERIMENTAL

The melting points were taken in open capillaries and are uncorrected. IR spectra (KBr in cm^{-1}) were recorded on Shimadzu 8201 PC FTIR spectrophotometer. ^1H NMR spectra were recorded on a Varian VXR-300SH

(300 MHz) NMR Spectrophotometer using DMSO-d_6 as solvent and TMS as internal standard (chemical shifts in δ ppm). The purity of the compounds was monitored by thin layer chromatography.

3-Cyano acetophenone (1): 3-Amino acetophenone (6.76 g, 0.05 mol) was added to a mixture of water (45 mL) and HCl (12 mL) followed by addition of sodium nitrite (3.45 g, 0.05 mol) dissolved in 7.2 mL water at 0°C. The reaction mixture was stirred for 1 h and then neutralized by 20 per cent sodium carbonate solution. The resulting mixture was then added into a mixture of sodium cyanide (8.0 g) and cuprous cyanide (7.2 g) in 30 mL water and then stirred for 1 h at room temperature. The product obtained was filtered, washed with water and crystallized from toluene to give 3-cyano acetophenone (**1**) (5.8 g, 80 %), m.p. 98°C (Found: C, 73.87; H, 4.25; N, 9.69. C_9H_7NO requires: C, 74.47; H, 4.86; N, 9.65 %).

3-Carboxy acetophenone (2): 3-Cyano acetophenone (**1**) (7.25 g, 0.05 mol) was slowly added to 75 % H_2SO_4 (100 mL) and refluxed for 8 h. The reaction mixture was then quenched into ice water. The compound obtained was filtered, washed with water and crystallized from ethanol to afford 3-carboxy acetophenone (**2**) (6.8 g, 83 %), m.p 169°C (Found: C, 65.79; H, 4.93. $C_9H_8O_3$ requires: C, 65.85; H, 4.91 %).

1-(3-Carboxy phenyl)-3-(4-substituted phenyl)-2-propene-1-ones (3a-e): To a mixture of compound **2** (8.2 g, 0.05 mol), 30 % sodium cumene sulphonate solution (10 mL, 0.013 mol), NaOH (2.0 g, 0.05 mol) and appropriate aromatic aldehyde (0.05 mol) was added and stirred at 30°C for 5 h. The product precipitated out was filtered, washed with warm water and recrystallized from ethanol to afford compound **3**.

Other propene-1-ones were prepared in an analogous manner. The melting points, yields and analytical data are given in Table-1.

TABLE-1
CHARACTERIZATION DATA OF 1-(3-CARBOXY PHENYL)-3-(4-SUBSTITUTED PHENYL)-2-PROPENE-1-ONES (**3a-e**)

Compd.	m.f.	R	Yield (%) / [m.p. (ºC)]	Elemental analysis: Calcd. (Found) %	
				C	H
3a	$C_{16}H_{12}O_3$	-H	91 [175]	76.18 (75.29)	4.79 (4.11)
3b	$C_{16}H_{11}O_3Cl$	-Cl	84 [168]	67.03 (66.82)	3.87 (3.94)
3c	$C_{17}H_{14}O_3$	$-CH_3$	82 [205]	76.68 (76.16)	5.30 (5.01)
3d	$C_{16}H_{12}O_4$	-OH	75 [164]	71.64 (72.04)	4.51 (4.72)
3e	$C_{17}H_{14}O_4$	$-OCH_3$	78 [185]	72.33 (71.91)	5.00 (5.19)

2-(3-Carboxy phenyl)-5-(4-substituted phenyl)-1-acetyl-2-pyrazolines (4a-e): The chalcone **3** (0.01 mol) was dissolved in glacial acetic acid (120 cm^3) and hydrazine hydrate (1.46 cm^3, 0.03 mol) was added. The reaction mixture was refluxed for 5 h and then poured into crushed ice. The resulting solid **4** was filtered, washed with water and crystallized from methanol. **4e:** IR (KBr) 2599 ν(O-H), 1682 ν(C=O), 1630 ν(C=N), 1254 ν(C-O-C); NMR (DMSO-d_6) δ 2.62 (s, 3H, -$COCH_3$), 2.94-2.99 (dd, 2H, -CH_2), 3.78 (s, 3H, -OCH_3), 5.41-5.46 (dd, 1H, -CH), 6.8-7.6 (m, 8H, ArH), 11.42 (s, 1H, -COOH); Mass m/z 356 (M^+), 313, 205, 191, 176, 160, 149, 134, 121, 106, 91(B), 77, 65.

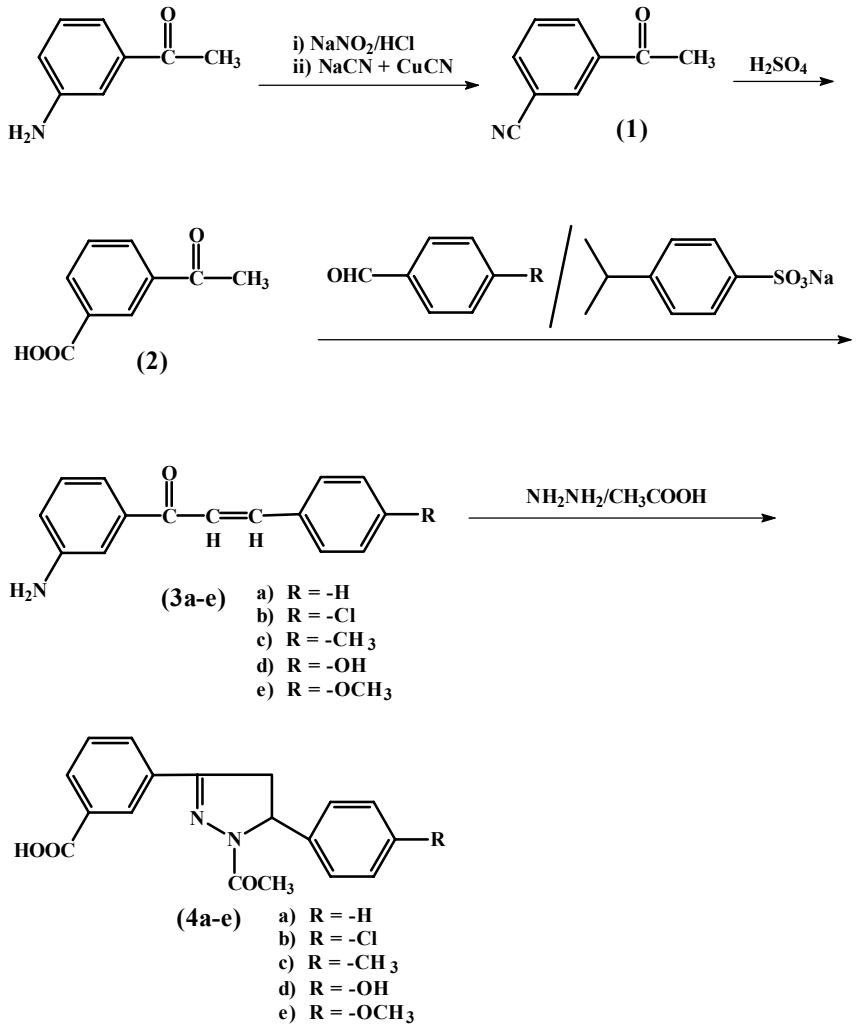
Other 1-acetyl-2-pyrazolines were obtained in a similar manner. The melting points, yields and analytical data are given in Table-2.

TABLE-2
CHARACTERIZATION DATA OF 2-(3-CARBOXY PHENYL)-5-(4-SUBSTITUTED PHENYL)-1-ACETYL-2-PYRAZOLINES (**4a-e**)

Compd.	m.f.	R	Yield (%) / [m.p. (ºC)]	Elemental analysis: Calcd. (Found) %	
				C	H
4a	$C_{16}H_{16}N_2O_3$	-H	75 [205]	70.12 (70.91)	5.23 (5.01)
4b	$C_{18}H_{15}N_2O_3Cl$	-Cl	65 [217]	63.07 (63.29)	4.41 (4.42)
4c	$C_{19}H_{18}N_2O_3$	-CH_3	78 [238]	70.79 (70.24)	5.63 (5.15)
4d	$C_{18}H_{16}N_2O_4$	-OH	69 [209]	66.66 (66.10)	4.97 (4.71)
4e	$C_{19}H_{18}N_2O_4$	-OCH_3	82 [211]	67.45 (67.92)	5.36 (5.49)

RESULTS AND DISCUSSION

3-Amino acetopheone was diazotised and reacted with sodium cyanide in presence of copper cyanide to yield 3-cyano acetopheone (**1**) which on further hydrolysis afforded 3-carboxy acetophenone (**2**). The compound (**2**) was condensed with various aromatic aldehydes in hydrotropic medium to give substituted chalcones (**3a-e**). Cyclization of the chalcones (**3a-e**) with hydrazine hydrate in glacial acetic acid yielded 2-(3-carboxy phenyl)-5-(4-substituted phenyl)-1-acetyl-2-pyrazolines (**4a-e**) (**Scheme-I**).



Scheme-I

Screening for biological activity: All the compounds **4a-e** were screened *in vitro* for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis* and *Salmonella typhosa* by the ditch-plate technique[6]. The compounds synthesized were also tested for antifungal activity against *Aspergillus niger*, *Candida albicans*, *Cryptococcus neoformans* and *Thielaviopsis paradoxa* by paper-disc diffusion method[7] using concentrations of 2 and 5 mg/mL. Nutrient agar was employed as culture media and DMF was used as solvent control for both antibacterial and antifungal activity. The result of such studies are given in Table-3.

TABLE-3
BIOLOGICAL ACTIVITY DATA

Compd.	Antibacterial activity (mg/mL)							
	S. aureus		*E. coli*		*B. subtilis*		*S. typhosa*	
	2	5	2	5	2	5	2	5
4a	+	+	-	+	+	+	+	+
4b	+	++	-	+	+	++	+	++
4c	-	+	-	+	-	+	-	+
4d	-	+	+	+	-	_	-	+
4e	+	+	+	++	-	-	-	+
Compd.	Antifungal activity (mg/mL)							
	A. niger		*C. albicans*		*C. neoformans*		*T. paradoxa*	
	2	5	2	5	2	5	2	5
4a	-	+	+	+	-	+	+	+
4b	-	+	-	+	+	+	+	++
4c	-	+	+	++	-	-	-	+
4d	+	++	_	-	-	+	-	-
4e	+	+	+	-	+	+	+	+

Inhibition zone diameter in mm: (-) < 11; (+) 11-14; (++) 15-18

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