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Synthesis and Antibacterial Activity of 3-Cyano-2-(1H)-Pyridone Derivatives

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Several new 3-cyano-4-substituted aryl-6-[2′-hydroxy-4′-(*p*-triflurometh yl/nitro-phenoxy)-phen-1′-y1]-2-(1H)-pyridone **(II)** have been prepared by reaction of 1-[2′-hydroxy-4′-(*p*-trifluoromethyl/nitro phenoxy)-phen-1′-y]-3-substituted aryl-2-propene-1-ones **(I)** with ethyl cyanoacetate and ammonium acetate in ethanol. Few of these compounds are characterized by IR and NMR spectra. All these synthesized 3-cyano-2-pyridones have been screened against a few microorganisms for antibacterial activity.

Key Words: Synthesis, Antibacterial, 3-Cyano-2-(1H) Pyridone derivatives

INTRODUCTION

Pyridine and its homologues are commonly called pyridine bases. Various derivatives of pyridine are of pharmaceutical and agrochemical interest. Some workers synthesized 3-cyano-2-(1H)-pyridone derivatives from chalcones and cyano acetamide[1], while some synthesized it from chalcone and ethylcyanoacetate and ammonium acetate[2,3]. Antibacterial[4], antifungal and molluscicidal activity[5] of 3-cyano-2-(1H)-pyridone derivatives were reported. Further, an introduction of fluorine atom or —CF_3 group into an organic molecule may alter the biological activities as reported[6]. Moreover 2-hydroxy-chalcones with —NO_2 group as an additional substituent are reported to exhibit very good antibacterial activity[7]. Therefore it was thought interesting to synthesize 3-cyano-2-(1H)-pyridones using ethyl cyanoacetate from chalcones containing —CF_3 and —NO_2 group in *p*-position of phenoxy substituent and to screen them as antibacterial agents.

EXPERIMENTAL

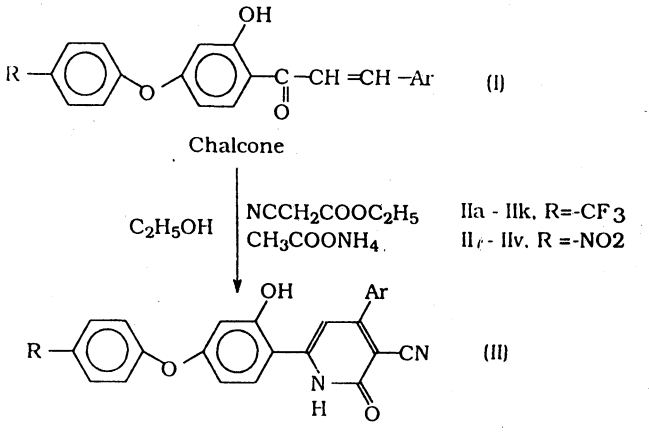
Preparation of 3-cyano-2-(1H)-pyridone derivatives

A mixture of chalcone (0.01 mol), ethyl cyanoacetate (0.01 mol) and ammonium acetate (0.08 mol) in ethanol (40 mL) was refluxed at 70–80°C on water bath for 6 h. It was then cooled and poured into ice-water. The product thus separated was filtered, washed with water, dried and crystallized from 1,4-dioxane.

Infrared spectra of the compounds were recorded in solid state using KBr pellet on Perkin-Elmer FT-IR spectrophotometer (Model-RX-1). The PMR spectra of

compounds were recorded in DMSO-d_6 solvent at room temperature using TMS as reference compound. The spectra were recorded on Perkin-Elmer Model-32 NMR spectrometer, at 300 MHz at CDRI Lucknow.

The antibacterial activities of the synthesized compounds and standard drugs (ampicillin and tetracycline) were screened by agar cup method in DMF solvent. The activity was checked against gram positive bacteria *B. subtilis* and *S. aureus* and gram negative bacteria *E. coli* and *S. typhi.*



RESULTS AND DISCUSSION

The main absorption bands observed in IR spectra are as under:

2230–2200 ν[C≡N]; 1710–1690 ν[C=O]; 3235–3200 ν[N—H]; 1575–1550 ν[N—H]; 1225–1200 ν[C—O—C]; 3455–3420 ν[O—H]; 1170–1150 ν[C—F]; 1535–1525 and 1375–1365 cm^{-1}ν[N=O] .

The position of signals in PMR spectra of compd. **IIr** can be assigned to different types of protons as under: δ = 10.25 (proton of —OH); δ = 3.80 (three protons of —OCH_3 group); δ = 6.27 to 8.00 (aromatic protons and proton of —NH).

Diameter of zone of inhibition (in mm) of standard drug ampicillin against *B. subtilis, S. aureus* (gram positive), *E. coli* and *S. typhi* (gram negative) were found to be 24, 22 17 and 16 respectively while tetracycline gave 18, 17, 21 and 22 respectively under identical conditions.

As compared to standards, among cyano-pyridones containing trifluoromethyl substitution compounds **IIb** and **IIk** containing 4-chloro-phenyl and 2-furyl substituent showed fairly good activity. Compounds **IIc, IId** and **IIe** containing 2-chloro-phenyl, 2,4-dichloro phenyl and 4-fluoro phenyl substituent respectively showed better activity than the previous two. Compound **IIa** containing phenyl substituent was found active against gram positive bacteria only. Compound IIh containing dimethoxy phenyl substituent was found inactive against *B. subtilis* and *S. typhi.* In case of nitro substituted cyano-pyridone compounds **IIp** and **IIr** containing 4-fluoro phenyl and 2-methoxy phenyl substituent showed maximum activity. Compounds **IIn** and **IIu** containing 2-chloro phenyl and 4-N,N-dimethylamino phenyl substituent showed moderate activity. Compound II

TABLE-1
DATA SHOWING CHARACTERISTICS OF COMPOUNDS (II) AND RESULTS OF ANTIBACTERIAL ACTIVITY

Compd. No.	R	Ar	m.w.	Yield (%)	m.p. (°C)	Elemental analysis % N		Antibacterial Activity			
								Gram positive		Gram negative	
						Found	Calculated	*B. subtilis*	*S. aureus*	*E. coli*	*S. typhi*
IIa	CF_3	$-C_6H_5$	448	60	254	6.14	6.25	x	x	7	9
IIb	CF_3	$-4-Cl-C_6H_4$	482.5	68	265	5.78	5.80	17	18	16	15
IIc	CF_3	$-2-Cl-C_6H_4$	482.5	66	260	5.74	5.80	19	20	18	21
IId	CF_3	$-2,4-(Cl)_2-C_6H_3$	517	67	271	3.39	5.41	21	17	19	20
IIe	CF_3	$-4-F-C_6H_4$	466	68	268	5.90	6.00	20	18	21	19
IIf	CF_3	$-4-OCH_3-C_6H_4$	478	65	258	5.69	5.85	9	6	10	7
IIg	CF_3	$-2-OCH_3-C_6H_4$	478	61	255	5.81	5.85	5	8	7	10
IIh	CF_3	$-3,4-(OCH_3)_2-C_6H_3$	508	65	279	5.40	5.51	x	6	9	x
IIi	CF_3	$-3,4,5-(OCH_3)_3-C_6H_2$	425	65	281	5.51	5.20	8	10	5	7
IIj	CF_3	$-4-\{N(CH_3)_2\}-C_6H_4$	491	66	270	8.51	8.55	10	6	9	5
IIk	CF_3	$-C_4H_3O-(2-furyl)$	438	64	261	6.29	6.39	16	17	16	17
III	NO_2	$-C_6H_4$	425	65	281	9.74	9.88	5	6	x	8
IIm	NO_2	$-4-Cl-C_6H_4$	459.5	71	296	9.09	9.14	9	7	10	7
IIn	NO_2	$-2-Cl-C_6H_4$	459.5	66	285	9.11	9.14	12	11	13	15
IIo	NO_2	$-2,4-(Cl)_2-C_6H_3$	494	72	> 300	8.47	8.50	8	5	9	6
IIp	NO_2	$-4-F-C_6H_4$	443	73	280	9.43	9.48	18	20	20	22
IIq	NO_2	$-4-OCH_3-C_6H_4$	455	68	> 300	9.15	9.23	8	x	7	5
IIr	NO_2	$-2-OCH_3-C_6H_4$	455	67	281	9.10	9.23	17	19	18	21
IIs	NO_2	$-3,4-(OCH_3)_2-C_6H_3$	485	72	274	8.59	8.65	9	10	7	5
IIt	NO_2	$-3,4,5-(OCH_3)_3-C_6H_2$	515	74	> 300	8.08	8.15	7	6	8	9
IIu	NO_2	$-4-\{N(CH_3)_2\}-C_6H_4$	468	71	269	11.88	11.96	14	10	11	12
IIv	NO_2	$-C_4H_3O-(2-furyl)$	415	70	260	10.08	10.12	8	9	6	x

x = Found inactive

containing phenyl substituent remained inactive against *E. coli*. Compound **IIq** containing 4-methoxy-phenyl substituent was found inactive against *S. aureus* while compound **IIv** containing 2-furyl substituent was found inactive against *S. typhi*.

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