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Research Article

Preparation Four Derivatives Compounds of acetyl-1*H*-pyrazole-4-carbaldehyde and Their Antimicrobial Activity

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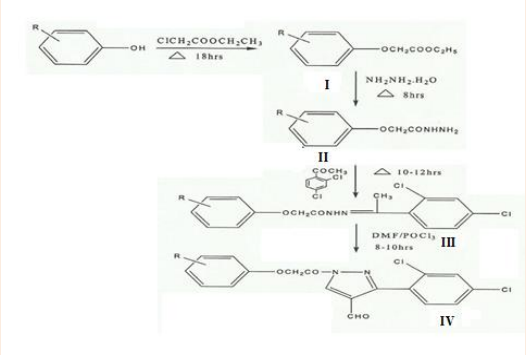
Abstract

Four derivatives compounds of acetyl-1*H*-pyrazole-4-carbaldehyde were prepared from substituted simple phenols. Substituted simple phenols were refluxed with ethylchloroacetate in the presence of anhydrous potassium carbonate to yield substituted ethyl phenoxy acetate. The treatment of ethyl phenoxy acetate with hydrazine hydrate in ethanol yielded substituted 2-phenoxyacetohydrazide in turn on refluxing with 2,4-dichloro acetophenones yielded *N*'-(1-(2,4-dichlorophenyl) ethylidene) -2-(substituted phenoxy) acetohydrazides which on further treatment with DMF and $POCl_3$ undergo Vilsmer -Haack reaction to yield the derivatives compounds of acetyl-1*H*-pyrazole - 4 - carbaldehyde. The chemical structures of these compounds were confirmed by various spectroscopic methods such as IR, ^{1}H-NMR, mass spectral data and elemental analysis. The prepared compounds were screened in vitro for their antimicrobial activity against bacterial strains (gram +ve and gram -ve) such as *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and fungi strains such as *Candida albicans* and *Aspergillus niger*. Antimicrobial activity was carried out by disc diffusion method. The inhibition zone shown by the compounds against selected microorganisms was measured by using antibiotic zone reader. The minimum inhibitory concentration was carried out for the compounds were determined by serial dilution method.



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Introduction

Azoles are compounds of five membered heterocyclic with additional hetero atom. Azoles containing two nitrogen atoms; one oxygen and one nitrogen atom; one sulfur and one nitrogen atom in the 1, 2-position are designated as pyrazole, isoxazole and isothiazole respectively. Many of the azoles comprise the ring system of several natural and synthetic compounds which are observed as vital for the human kind as drugs, dyes and pesticides [1]. Pyrazole was first described by Buchner in 1889 during the decomposition of pyrazole 3, 4, 5-carboxylic acid. The dihydro pyrazoles are called pyrazolines and depending on the position of the double bond three forms of pyrazolines are possible. These are 1-pyrazoline, 2-pyrazoline and 1, 3-pyrazoline. Pyrazoles are more stable than pyrazolines and can be converted into the later by mild oxidizing agents like bromine and lead tetra acetate. Pyrazole is a colorless solid with melting point 70°C and is soluble in water. It possesses penetrating smell unlike most of the amines. Pyrazole has a high boiling point 187°C and it can be synthesized by various methods in which the most important method is the reaction between 1, 3-dicarbonyl compound and hydrazine. A simple pyrazole is obtained with 1, 3-dicarbonyl compound such as acetyl acetone and hydrazine hydrate. Pyrazoles can also be prepared from α, ß-ethylene carbonyl derivative and α, ß-acetylene carbonyl compounds. In this case the hydrazine may form hydrazone or add directly to the acetylenic bond. Pyrazole carbaldehydes can be prepared via hydrazones by Vilsmeir-Hack

reaction. Vilsmeir-Hack reaction is a cyclic reaction that takes place in the presence of DMF/$POCl_3$ often referred as Vilsmeir-Hack reagent [2]. Pyrazoles can prepared on solid supports by using catch-release solid phase strategy [3]. The condensation of the carbonyl function in pyrazole carbaldehydes with some active methylene groups can be carried out under ultrasound irradiation which results in biologically important compounds [4]. Pyrazole and pyrazole carbaldehyde derivatives coupled with other heterocyclic compounds like 1, 8-naphthyridine, benzopyrans, anthracene, pyrimidine, benzofuran…..etc, are reported to possess antibacterial and antifungal activities [5-12]. The pyrazole derivatives were also reported to possess mono amino oxidase inhibitory activity [13-14]. Pyrazole-related nucleosides were reported to show antiviral, antitumor activities [15]. Pyrazole derivatives were also reported to possess helicobacter pyrolidihydroorotate dehydrogenase inhibitory activity [16]. 3-(4-phenoxyphenyl) pyrazoles were reported as a novel class of sodium channel blockers [17]. Pyrano pyrazole derivatives were reported with molluscicidal activity [18]. Pyrazoles were also reported to possess cytotoxic [19-20] and cannabinod-1 receptor antagonist [21], anti convulsant [22] activities. Pyrazole-4-carboxamides were reported to possess anti-leukemic activity [23]. Apart from that pyrazole derivatives were also found to possess AT-1 antagonistic, DNA gyrase inhibitory and antileukemic properties [24].

Materials and Methods

Melting points were taken in open capillaries and are uncorrected. Infra-red spectra (KBr/cm^{-1}) were recorded on 8400S, Shimadzu FT-IR spectrophotometer.

^{1}H-NMR spectra were measured by Bruker Ascend-TM 400MHz-NMR spectrometer, deuterated solvents such as dimethyl- sulphoxide (DMSO-d_6), methanol (CD_3OD) and also chloroform ($CDCl_3$) were used as solvents and the chemical shifts were quoted as δ-value relative to tetramethyl silane (TMS, δ=0) as an internal standard. Mass spectra were recorded on LC-MS Schimadzu 2010A spectrometer. The elemental analysis was carried out on a Perkin Elmer C, H, N analyzer. The purity of the compounds was monitored by thin layer chromatography on silica gel plates and iodine was used as a visualizing agent.

3-(2, 4-dichlorophenyl)-1-(2-phenoxyacetyl)-1*H*-pyrazole-4-carbaldehyde (I)

A mixture of phenol (0.04 mol) and ethylchloroacetate (0.05 mol) was refluxed in dry acetone in presence of potassium carbonate for 24 hours on water bath. The reaction mixture was cooled and filtered, the excess solvent was distilled and the solid thus separated was recrystallized from ethanol to yield compound I.
IR (KBr/cm^{-1}): 3013.89 (Ar-H str), 1667.81 (C=O str) 1594.23 (C=N of ringstr.), 1484.00 (Ar-C=C str), 1198.07 (C-O-C str), 756.09 (C-Cl str). ^{1}H-NMR (400 MHz, ppm): 9.3 (s, 1H, -CHO), 8.0-6.5 (m, 9H, Ar-H), 5.3 (s, 2H, OCH_2). MS (m/z): 376 (M^+); Anal. Calcd (found) for $C_{18}H_{12}Cl_2N_2O_3$, C, 57.60 (56.56); H,3.20 (3.07); N, 6.40 (6.36).

1-(2-(4-chlorophenoxy) acetyl)-3-(2,4-dichlorophenyl)-1*H*-pyrazole-4-carbaldehyde (IV)

0.004 mol of compound III was dissolved in Vilsmeier -Haack reagent (DMF - 10 ml and $POCl_3$ - 4 ml) and stirred at room temperature for 8-10 hours. The contents were poured onto crushed ice and neutralized with NaHCO3, the Solid thus separated was filtered, washed with cold water, dried and recrystallized from DMF to give compound IV.
IR (KBr/cm^{-1}): 3007.89 (Ar-H str), 1686.81(C=O str) 1596.23 (C=N of ring str.), 1485.00 (Ar-C=C str), 1197.07 (C-O-C str), 754.00 (C-Cl str). ^{1}H-NMR (400 MHz, ppm): 9.4 (s, 1H, - CHO), 8.0-6.5 (m, 8H, Ar-H), 5.2 (s, 2H OCH_2). MS (m/z): 410 (M^+); Anal. Calcd (found) for $C_{18}H_{11}Cl_3N_2O_3$, C, 52.81 (51.79); H, 2.68 (2.66); N, 5.86 (5.83).

3-(2,4-dichlorophenyl)-1-(2-(2,4,6-trichlorophenoxy)acetyl)-1*H*-pyrazole-4-carbaldehyde (II)

A mixture of compound I (0.05 mol) and hydrazine hydrate (0.08 mol) in ethanol were refluxed for 8 hours. The excess of solvent is distilled off and the solid thus separated was recrystallized from ethanol to give compound II.

IR (KBr/cm^{-1}): 3043.89 (Ar-H str), 1691.81(C=O str) 1556.23 (C=N of ring str.), 1483.00 (Ar-C=C str), 1198.07 (C-O-C str), 756.37(C-Cl str). ^{1}H-NMR (400 MHz, ppm): 9.3 (s, 1H, -CHO), 8.0-6.5 (m, 6H, Ar-H), 5.3 (s, 2H, OCH_2). MS (m/z): 479 (M^+); Anal. Calcd (found) for $C_{18}H_9Cl_5N_2O_3$, C, 45.18 (44.15); H, 1.88 (1.00); N, 5.02 (5.00).

3-(2,4-dichlorophenyl)-1-(2-(4-hydroxyphenoxy) acetyl-1*H*-pyrazole-4-carbaldehyde (III)

A mixture of compound III (0.03 mol) and 2,4-dichloro acetophenone (0.03 mol) was refluxed along with a few drops of glacial acetic acid for 10-12 hours. The reaction mixture was cooled and then poured on to crushed ice and stirred well. The separated solid was filtered and recrystallized from ethanol to yield compound III.
IR (KBr/cm^{-1}): 3304.07 (OH str), 3009.89 (Ar-H str), 1698.81 (C=O str) 1589.07 (C=N of ring str.), 1488.84 (Ar-C=C str), 1194.07 (C-O-C str), 756.78 (C-Cl str). ^{1}H-NMR (400 MHz, ppm): 11.3 (s, 1H, OH), 9.4 (s, 1H, -CHO), 8.0-6.5 (m, 8H, Ar-H), 5.3 (s, 2H, OCH_2). MS (m/z): 392 (M^+); Anal. Calcd (found) for $C_{18}H_{12}Cl_2N_2O_4$, C, 55.24 (54.22); H, 3.06 (3.00); N, 6.13 (6.11).

Antimicrobial activity

Four prepared compounds were screened in vitro for their antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli* by disc diffusion method [14] using Mueller, Hinton agar (Hi-Media) medium. Each compound was tested at a concentration of 20 µg/ml in DMSO. The diameter of inhibition zone was measured in mm after 24 hours incubation at 37˚C. The known compound ciprofloxacin was used as standard drug for comparison study. The antibacterial screening data are recorded in Table 2. The compounds were evaluated for their in vitro antifungal activity against *Candida albicans* and *Aspergillus nigar* using disc diffusion method [15] with sabouraud's dextrose agar (Hi-Media). Each compound was tested at a concentration of 20 µg/ml in DMSO. The inhibition zone was measured in (mm). The known compound Amphotericin B was used as standard drug for comparison study. The antifungal activity are reported in Table 2.

Results and Discussion

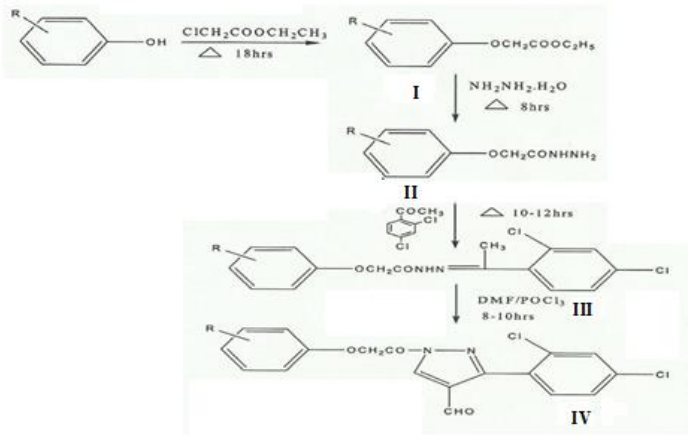

Figure 1 Preparation four derivatives compounds of acetyl-1H-pyrazole-4-carbaldehyde (I, II, III and IV)

All the prepared compounds are crystalline solids and the compounds obtained were having pale yellow to light brown in color and the melting points are reported in Table 1. The compounds are insoluble in water and common organic solvents, but readily soluble in DMF and DMSO. Preparation the derivatives of pyrazole-4-carbaldehyde by the above described method as shown in Figure I resulted in products with good yield. The solvents and reagents used in this work were of laboratory grade and were purified by distillation. The structures of the prepared compounds were established on the basis of spectral data such as IR, ^{1}H-NMR and mass spectroscopy. The prepared pyrazole-4-

carbaldehyde was tested for antimicrobial activity against *B. subtilis*, *p. aerugenosa*, *E. coli*, *S. aureus*, *C. albicans* and *A. nigar* showed moderate to significant activity. Compounds I, II, III and IV having phenyl, -OH, -Cl and -CHO groups have shown moderate to significant activity against some of the selected bacteria and fungi. This indicates that the compounds that have chloro substituent have shown wide spectrum of antimicrobial activity. Ciprofloxacin and Amphoterecin B were used as a standard drug. Minimum inhibitory concentration was carried out for compounds have shown activity at 20µg/ml.

Table 1 Physical data for the derivatives of pyrazol-4-carbaldehyde

Compounds	Molecular formula	M.W	M.P. °C	Yields (%)
I	$C_{18}H_{12}Cl_2N_2O_3$	376	138-140	64
II	$C_{18}H_9Cl_5N_2O_3$	479	184-185	53
III	$C_{18}H_{12}Cl_2N_2O_4$	392	162-164	84
IV	$C_{18}H_{11}Cl_3N_2O_3$	410	148-152	75

Table 2 Antimicrobial activity of the derivatives of pyrazol-4-carbaldehyde

Compounds	*B. subtilis*	*S. aureus*	*P. aeruginosa*	*E. coli*	*C. albicans*	*A. niger*
I	10	10	22	28	12	14
II	10	7	16	11	10	12
	20	25	24	18	13	13
IV	13	15	18	14	8	7
Amphotericin B	-	-	-	-	18	20
Ciprofloxacin	24	22	24	20	-	-

Conclusion

Preparation of pyrazole-4-carbaldehyde derivatives by the above described method resulted in the products with good yield. The structures of the prepared compounds were confirmed on the basis of spectral and elemental analysis data. Pyrazole-4-carbaldehyde derivatives are showing moderate to highly significant antimicrobial activity against all tested microorganisms.

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