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Synthesis, Characterization and Antibacterial Activity of some 1-Heteroaryl-3-aryl-1*H*-pyrazole-4-carbaldehydes

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ABSTRACT

Synthesis of some 4-formylpyrazoles has been described bearing heteroaryl moiety at N1 from differently substituted acetophenone hydrazone derivatives using Vilsmeier-Haack reagent. The structure of the synthesized compounds was established using FT-IR, ^{1}H & ^{13}C-NMR and HRMS spectral data. *In vitro* antibacterial activity studies indicated that compounds **3c, 3f** and **3i** have significant activity against *S. aureus* (MIC range = 0.44–0.58x10^{-2} µM/ml) and *E.coli* (MIC range = 0.48–0.89x10^{-2} µM/ml).

Keywords: Pyrazole; formylation; carbaldehyde; antibacterial activity.

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INTRODUCTION

Pyrazole derivatives enjoy a unique place in heterocyclic chemistry because of their potential to display wide range of biological activities [1]. There are several reviews available on the synthesis of pyrazoles utilizing different route as they serve as precursor for the production of important biologically active molecules [2]. Pyrazoles with various functional groups at different positions have been identified to show good agricultural and pharmaceutical activities. Recent literature survey disclosed that a number of biologically active compounds have been synthesised using pyrazole-3(4)-carbaldehydes [3]. The application of Vilsmeier-Haack reagent for formylation and various chemical transformation of aryl and heteroaryl substrate are well known [4]. Prompted by above observations, we report herein synthesis of some 4-formylpyrazoles possessing heteroaryl moiety at N1 from differently substituted acetophenone hydrazone derivatives using Vilsmeier-Haack reagent. The spectral studies of the synthesized compounds were thoroughly studied. They were also tested *in vitro* for their antibacterial activity against Gram-positive (*B. subtilis*, *S. aureus*) and Gram-negative bacteria (*E. coli*).

MATERIAL AND METHODS

Melting points were determined in open capillaries and are uncorrected. FTIR spectra were recorded in potassium bromide on IR Affinity-I (Shimadzu) spectrophotometer and are reported in cm^{-1}. ^{1}H and ^{13}C NMR spectra were scanned on a Bruker Avance III NMR spectrometer operating at 400 MHz in $CDCl_3$ and are expressed as ppm with respect to TMS. HRMS were recorded on the 6500 series Agilent Accurate-Mass Q-TOF LC/MS system.

General method for the preparation of 1-heteroaryl-3-aryl-1*H*-pyrazole-4-carbaldehyde (3):

The appropriate acetophenone derivatives (**1**) (1 mmol) was added heteroarylhydrazines (1 mmol) in methanol followed by addition of few drop of acetic acid and the reaction mixture was refluxed for 2 hr. After completion reaction mixture was cooled to room temperature and solid so precipitate was filtered and washed with cold methanol. The crude hydrazones (**2**) (1 mmol) was added to cold solution of dimethylformamide (25 ml) and phosphorous oxy chloride (5 ml), and the resulting mixture was stirred at 50-60 °C for 4-5 hrs, then cooled to room temperature and poured on to crushed ice. Excess acid was neutralized by adding saturated sol. of sodium bicarbonate resulting 4-formylpyrazoles (**3a-3i**) which were filtered and washed with cold water.

3-Phenyl-1-(4-phenylthiazol-2-yl)-1H-pyrazole-4-carbaldehyde (3a)

mp: 165-166 °C yield: 73% ; IR(KBr)ν: 3062, 3028, 2873, 2827, 2777, 2748, 1691, 1672, 1645, 1510, 1479 cm^{-1}; NMR δ_H (400 MHz, $CDCl_3$): 10.09 (s, 1H, CHO), 9.05 (s, 1H, C_5-H), 7.92-7.85 (m, 4H, ArH), 7.57-7.36 (m, 7H, Ar-H); NMR δ_C (100 MHz, $CDCl_3$): 184.6, 159.4, 155.3, 153.2, 133.5, 131.8, 130.5, 129.8, 129.0, 128.9, 128.8, 128.7, 126.1, 122.8, 110.7; HRMS: m/z (M^+) calcd. for $C_{19}H_{13}N_3OS$: 331.0799, found: 332.0798 (M+H).

1-(4-Phenylthiazol-2-yl)-3-p-tolyl-1H-pyrazole-4-carbaldehyde (3b)

mp: 138-139 °C yield: 72% ; IR(KBr)ν: 2951, 2916, 2827, 2720, 1718, 1693, 1678, 1537, 1521, 1510, 1479 cm^{-1}; NMR δ_H (400 MHz, $CDCl_3$): 10.07 (s, 1H, CHO), 9.03 (s, 1H, C_5-H), 7.93-7.90 (m, 4H, ArH), 7.79-7.73 (m, 4H, ArH), 7.47-7.35 (m, 2H, Ar-H), 2.43 (s, 3H, CH_3); NMR δ_C (100 MHz, $CDCl_3$): 184.7, 159.4, 155.3, 153.1, 133.6, 131.7, 129.5, 129.3, 128.9, 128.7, 128.4, 128.1, 126.1, 122.8, 110.7, 21.4; HRMS: m/z (M^+) calcd. for $C_{20}H_{15}N_3OS$: 345.0936, found: 346.0833 (M+H).

3-(4-Fluorophenyl)-1-(4-phenylthiazol-2-yl)-1H-pyrazole-4-carbaldehyde (3c)

mp: 217-218 °C yield: 71% ; IR(KBr)ν: 3103, 2850, 2762, 1722, 1693, 1600, 1541, 1514, 1479 cm^{-1}; NMR δ_H (400 MHz, $CDCl_3$): 10.07 (s, 1H, CHO), 9.06 (s, 1H, C_5-H), 7.94-7.90 (m, 4H, ArH), 7.49-7.38 (m, 4H, Ar-H), 7.26-7.18 (m, 2H, ArH); NMR δ_C (100 MHz, $CDCl_3$): 184.0, 163.5 (d), 159.2, 153.8, 153.1, 133.4, 132.9, 131.0 (d), 128.8, 128.7, 126.6, 126.1, 122.7, 115.7 (d), 110.8; HRMS: m/z (M^+) calcd. for $C_{19}H_{12}FN_3OS$: 349.0685, found: 350.0583 (M+H).

1-(Benzo[d]thiazol-2-yl)-3-phenyl-1H-pyrazole-4-carbaldehyde (3d)

mp: 226-228 °C yield: 62% ; IR(KBr)ν: 3128, 3059, 3034, 2962, 2908, 2825, 2725, 1685, 1639, 1604, 1554, 1492 cm^{-1}; NMR δ_H (400 MHz, $CDCl_3$): 10.11 (s, 1H, CHO), 9.10 (s, 1H, C_5-H), 7.90-7.87 (m, 3H, ArH), 7.54-7.43 (m, 5H, Ar-H).

1-(Benzo[d]thiazol-2-yl)-3-p-tolyl-1H-pyrazole-4-carbaldehyde (3e)

mp: 134-135 °C yield: 60% ; IR(KBr)ν: 3107, 3059, 3026, 2991, 2941, 2912, 2850, 2725, 1697, 1683, 1633, 1602, 1514, 1446 $cm^{-1.}$.

1-(Benzo[d]thiazol-2-yl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (3f)

mp: 187-188 °C yield: 60% ; IR(KBr)ν: 3147, 3103, 2850, 2762, 1737, 1693, 1658, 1602, 1541, 1514 cm^{-1}; NMR δ_H (400 MHz, $CDCl_3$): 10.07 (s, 1H, CHO), 9.05 (s, 1H, C_5-H), 7.95-7.90 (m, 4H, ArH), 7.48-7.45 (m, 2H, Ar-H), 7.22-7.18 (m, 2H, ArH); NMR δ_C (100 MHz, + DMSO-d_6): 184.0, 163.7 (d), 159.3, 153.9, 153.2, 133.5, 132.8, 131.0 (d), 128.9, 128.7, 126.1, 122.7, 115.8 (d), 112.5, 110.8.

3-Phenyl-1-(pyridin-2-yl)-1H-pyrazole-4-carbaldehyde (3g)

mp: 105-106 °C yield: 69% ; IR(KBr)ν: 3093, 3057, 3030, 2931, 2850, 2821, 2736, 1689, 1651, 1597, 1510, 1444 cm^{-1}; NMR δ_H (400 MHz, $CDCl_3$): 10.08 (s, 1H, CHO), 9.20 (s, 1H, C_5-H), 8.48 (d, 1H, J = 4.0 Hz, C_2-H Py), 8.13 (d, 1H, J = 8.4 Hz, PyH), 7.91-7.87 (m, 4H, Ar-H), 7.52-7.48 (m, 2H, ArH), 7.31-7.30 (m, 1H, ArH); NMR δ_C (100 MHz, $CDCl_3$): 184.9, 154.7, 150.4, 148.4,

147.5, 138.9, 138.2, 132.3, 131.3, 128.9, 128.7, 122.8, 113.1; HRMS: m/z (M^+) calcd. for $C_{15}H_{11}N_3O$: 249.0902, found: 250.0804 (M+H).

1-(Pyridin-2-yl)-3-p-tolyl-1H-pyrazole-4-carbaldehyde (3h)

mp: 95-96 °C yield: 65% ; IR(KBr)ν: 3080, 3030, 2966, 2943, 2864, 2831, 2750, 2341, 1720, 1676, 1597, 1575, 1473 cm^{-1}; NMR δ_H (400 MHz, $CDCl_3$): 10.08 (s, 1H, CHO), 9.18 (s, 1H, C_5-H), 8.48 (d, 1H, J = 4.0 Hz, PyH), 8.12 (d, 1H, J = 8.1 Hz, PyH), 7.90-7.86 (m, 1H, PyH), 7.77 (d, 2H, J = 7.8 Hz, Ar-H), 7.33-7.28 (m, 3H, ArH), 2.43 (s, 3H, CH_3); NMR δ_C (100 MHz, $CDCl_3$): 185.0, 154.8, 150.4, 148.4, 139.5, 138.9, 132.2, 129.4, 129.1, 128.8, 128.4, 122.7, 113.1, 21.4; HRMS: m/z (M^+) calcd. for $C_{16}H_{13}N_3O$: 263.1059, found: 264.0989 (M+H).

3-(4-Fluorophenyl)-1-(pyridin-2-yl)-1H-pyrazole-4-carbaldehyde (3i)

mp: 137-138 °C yield: 68% ; IR(KBr)ν: 3097, 3066, 3008, 2941, 2854, 2725, 1712, 1687, 1598, 1579, 1456 cm^{-1}; NMR δ_H (400 MHz, $CDCl_3$): 10.06 (s, 1H, CHO), 9.19 (s, 1H, C_5-H), 8.48 (d, 1H, J = 4.0 Hz, PyH), 8.10 (d, 1H, J = 8.0 Hz, PyH), 7.91-7.87 (m, 4H, Ar-H), 7.30-7.14 (m, 2H, ArH); NMR δ_C (100 MHz,$CDCl_3$): 184.4, 164.5 (d), 156.9, 150.3, 148.4, 139.0, 138.4, 133.4, 130.9 (d), 127.5, 122.3, 115.6 (d), 113.0; HRMS: m/z (M^+) calcd. for $C_{15}H_{10}FN_3O$: 267.0808, found: 268.0906 (M+H).

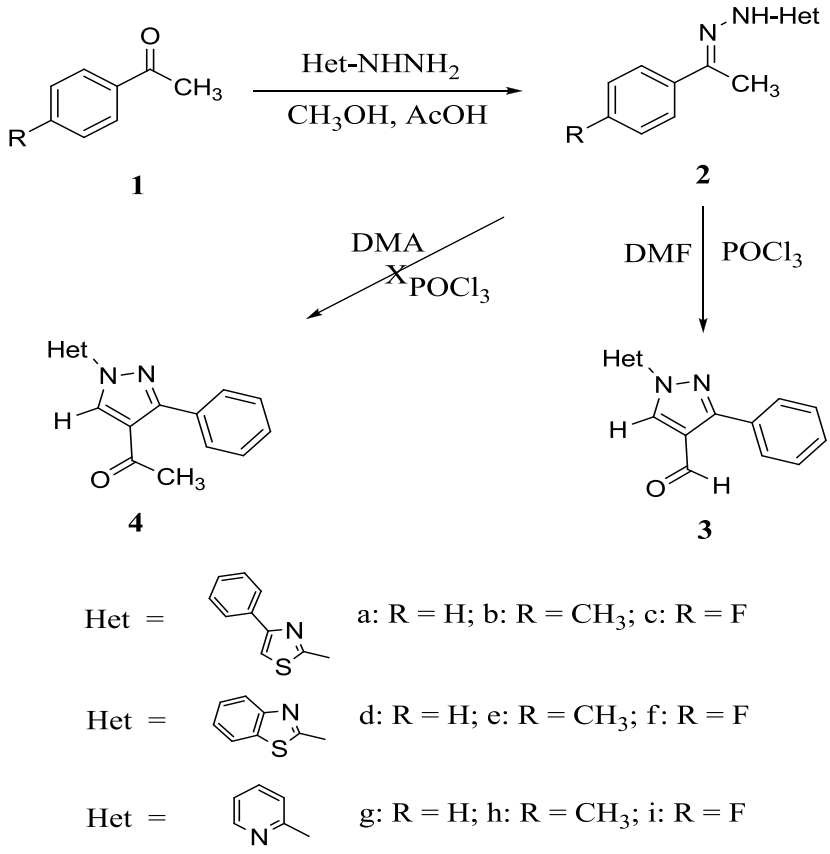
Evaluation of antibacterial activity (Determination of MIC)

The antibacterial activity of all the 1-heteroaryl-3-aryl-1*H*-pyrazole-4-carbaldehydes **(3a-3i)** was performed against Gram-positive bacteria: *Staphylcococcus aureus* [MTCC 2901], *Bacillus sublitis* [MTCC 2063] and Gram-negative bacteria: *Escherichia coli* [MTCC 1652] using tube dilution method. Dilutions of test and standard compounds were prepared in double strength nutrient broth – I.P. The samples were incubated at 37°C±1°C for 24 h and the results were recorded in terms of MIC.

RESULTS AND DISCUSSION

The methanolic solution of differently acetophenone (**1a**) was refluxed with 2-hydrazino-4-phenylyhiazole containing catalytic amount of acetic acid to get the hydrazone (**2a**). The hydrazone (**2a**) thus obtained was subjected to Vilsmeier-Haack condition (DMF-$POCl_3$ at 60-65°C for 6-8 h) that resulted in the formation of the 4-formylpyrazole (**3a**) in 73% yield (Scheme 1). The structure of **3a** was thoroughly studied using FTIR, NMR and HRMS techniques. The IR spectrum of **3a** exhibited different bands at 3062, 3028, 2873, 2777 cm^{-1} due to C-H stretching (aromatic and aliphatic), 2827, 2748 cm^{-1} due to C-H stretching of CHO (Fermi resonance) and 1691 due to C=O stretching of CHO besides other bands. In ^{1}H NMR spectrum, the aldehydic proton appeared at δ 10.09 and proton at C_5-H of pyrazole resonated at δ 9.05 besides other aromatic protons. The deshielding of the proton at C_5-H of pyrazole may be

attributed to the presence of thiazolyl moiety at N_1 of pyrazole. In ^{13}C NMR of **3a** the carbons at δ 153.2, 110.7 and 131.8 were assigned to C-3, C-4 and C-5 respectively.



Scheme 1

In order to generalize the procedure for the formation of 4-formypyrazole (**3**), differently substituted acetophenones (**1b-1c**) were refluxed with equimolar 2-hydrazinothiazole and 2-hydrazinopyridine containing catalytic amount of acetic acid to get the hydrazones (**2b-2i**). The hydrazones (**2b-2i**) were similarly subjected to Vilsmeier-Haack condition for the formation of the 4-formylpyrazoles (**3b-3i**) in good yield (Scheme 1). The structure of 4-formylpyrazoles was thoroughly studied using FTIR, NMR and HRMS techniques.

The FTIR spectra of compounds **3b-3i** showed the bands at ~2820 and 2720 cm^{-1} indicating the presence of C-H stretching of aldehyde group due to Fermi resonance and C=O stretching band at ~ 1710 cm^{-1} besides other bands. The ^1H NMR spectra of **3a-3c** having 2-thazolyl group, **3d-3f** having 2-benzothiazolyl group and **3g-3i** having pyridyl group at N1 of pyrazole exhibited interesting pattern for C_5-H and aldehydic proton at C_4 of pyrazole as shown in the Fig. 1. The deshielding of proton at position-5 of pyrazole from δ 9.05 to 9.10 to 9.19 may be attributed to the heteroaryl moiety (thiazolyl/benzothiazolyl/pyridyl) at position-1 of pyrazole. There was minor variation in the chemical shift value of aldehydic proton on changing the heteroaryl moiety.

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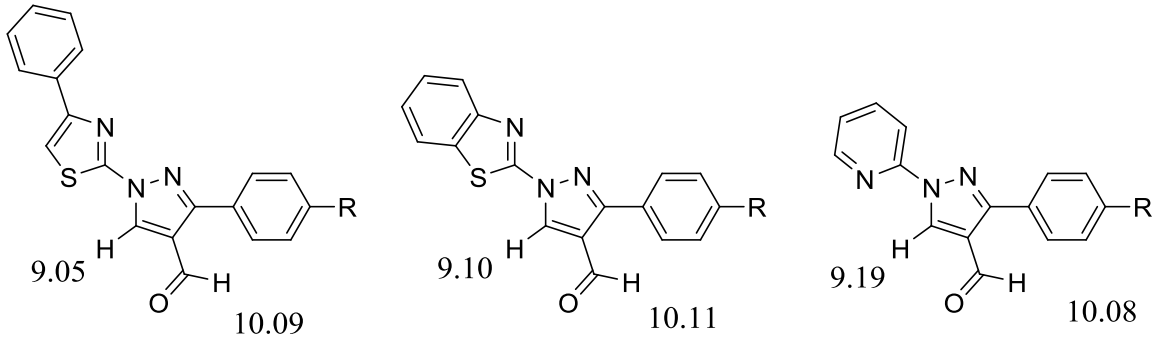

Fig. 1

Further, in order to bring acetyl group at position-4 of the pyrazole, the hydrazones (**3**) were treated with dimethyl acetaamide instead of DMF in $POCl_3$ under VH reaction conditions. This reaction did not result in the formation of 4-acetylpyrazoles (**4**).

Antibacterial activity

The antibacterial activity of all the 1-heteroaryl-3-aryl-1*H*-pyrazole-4-carbaldehyde **(3a-3i)** was performed against Gram-positive bacteria: *Staphylcococcus aureus* [MTCC 2901], *Bacillus sublitis* [MTCC 2063] and Gram-negative bacterium: *Escherichia coli* [MTCC 1652]. Double strength nutrient broth-I.P [5]. was employed for bacterial activity. Minimum inhibitory concentrations [MIC] were determined by means of standard serial dilution [6] and are presented in Table 1.

Table 1. *In vitro* antibacterial activity of pyrazol-4-carbaldehde (3a-3i)

MIC(10^{-2}μM/ml)

Compounds	*S. aureus*	*B. subtilis*	*E. coli*
3a	1.88	1.88	0.94
3b	1.88	3.62	3.62
3c	0.44	0.89	0.89
3d	1.02	1.02	2.04
3e	3.91	1.95	1.95
3f	0.48	0.96	0.48
3g	1.25	1.25	0.62
3h	1.18	1.18	0.59
3i	0.58	1.16	0.58
Ciprofloxacin	0.94	0.94	0.94

Results of antibacterial activity (Table 1) demonstrated that compounds **3c, 3f** and **3i** have significant activity against *S. aureus* (MIC range = 0.44–0.58x10^{-2} µM/ml) and *E.coli* (MIC range = 0.48–0.89 x 10^{-2} µM/ml), **3c** and **3f** were the most potent ones among the synthesized compounds against *B. subtilis* (MIC range = 0.89–0.96 x 10^{-2} µM/ml).

CONCLUSIONS

In summary, we have synthesized some 4-formylpyrazoles bearing heteroaryl moiety at N1 from differently substituted acetophenone derivatives using Vilsmeier-Haack reagent. The structure of the synthesized compounds was established using FT-IR, ^{1}H & ^{13}C-NMR and HRMS spectral data. *In vitro* antibacterial activity studies indicated that compounds **3c, 3f** and **3i** have significant antibacterial activity against *S. aureus* (MIC range = 0.44–0.58 x 10^{-2} µM/ml) and *E.coli* (MIC range = 0.48–0.89 x 10^{-2} µM/ml), **3c** and **3f** were the most potent ones among the synthesized compounds against *B. subtilis* (MIC range = 0.89–0.96 x 10^{-2} µM/ml).

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