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RESEARCH ARTICLE

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Synthesis and bactericidal activities of novel pyrazole-1-carbothioamide derivatives

Abstract 4-(2-Hydroxy-phenyl)-but-3-en-2-one (**1**) was prepared *via* condensation of salicylaldehyde with acetone, and then reaction of the ketone **1** with thiosemicarbazide was accompanied by cyclization to give substituted pyrazole (**2**). Seven new 5-(2-hydroxy-phenyl)-3-methyl-4,5-dihydropyrazole-1-carbothioamide derivatives (**3a**−**3g**) were synthesized by the acylation of **2** and characterized by means of elemental analysis, infrared (IR), and ^{1}H nuclear magnetic resonance (NMR). The compounds **3c**, **3d**, and **3g** showed certain bactericidal activity against *E. coli*; while compound **3g** showed certain bactericidal activity against *P. vulgaris*.

Keywords pyrazole, carbothioamide, bioactivity

1 Introduction

Recently, pyrazole derivatives have attracted considerable attention in agrochemical and medicinal research, since these compounds have been found to possess good bioactivities such as anti-tumor, anti-senile dementia, antibacterial, anti-viral, and anticonvulsive activities [1−7]. Screening of thioamides for new antibiotics has been reported [8−10]. A large number of investigations on their synthesis and biological activities have appeared during the past two decades. However, little attention has been paid to the synthesis of pyrazole bearing 5-phenyl moiety. In our previous work, we reported that some 5-(2-hydroxy-phenyl)-3-methyl aminopyrazole derivatives showed fungicidal activities [11−16]. Based on the theory of structure-activity relationship, we design and synthesized a series of 5-(2-hydroxy-phenyl)-3-methyl-4,5-dihydropyrazole-1-carbothioamide derivatives [17,18]. The structures of these compounds were characterized by means of elemental analysis, infrared (IR) and ^{1}H nuclear magnetic resonance (NMR), and their bactericidal activities were tested preliminarily. The synthesis route to these derivatives is shown in Scheme 1.

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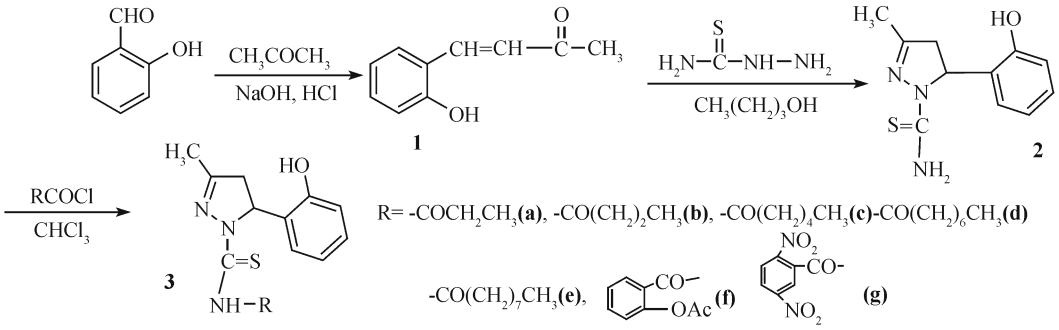
2 Experimental

2.1 General

All melting points were uncorrected. 2-Hydroxyphenyl-α, β-unsaturated ketone (**1**) was synthesized according to the literature [19], mp: 135°C−136°C (literature: 136°C−138°C); yield: 79.2%. A Varian INOVA400 (400 MHz) pulse Fourier-transform NMR spectrometer in $CDCl_3$ was used to record ^{1}H NMR spectra, using tetramethylsilane as an internal standard, and a Bruker Vector22 spectrometer was used to record IR spectra (KBr). Elemental analysis was performed using a Vario-III carbon, hydrogen, and nitrogen (CHN) analyzer. The reagents were analytically or chemically pure.

2.2 5-(2-Hydroxy-phenyl)-3-methyl-4,5-dihydropyrazole-1-carbothioamide (**2**)

To a three-necked 100 mL flask were added 1.62 g (10 mmol) α, β-unsaturated ketone 1, 0.91 g (10 mmol) thiosemicarbazide, and 30 mL l butanol. The mixture was heated under reflux for 4 h and then stirred at 20°C for 6 h. The reaction was monitored by thin layer chromatography (TLC) (V(acetone): V(petroleum ether 60°C−90°C) = 1:1) and stopped when TLC showed only one spot with $R_f = 0.58$. The reaction mixture was filtered to give pale yellow solid. The solid was washed with petroleum ether and then recrystallized in ethanol to give **2** as colorless solid (1.17 g).



Scheme 1 Synthesis route to pyrazole-1-carbothioamide derivatives

2.3 5-(2-Hydroxy-phenyl)-3-methyl-4, 5-dihydropyrazole-1-carbothioamide derivatives (**3**)

In a 50 mL three-necked round-bottom flask, 0.60 g (2.55 mmol) compound **2** was mixed with pyridine (3.0 mL), and then dry chloroform (30 mmol) was added. The resulting solution was stirred and cooled to 0°C−5°C with an ice bath. A solution of chloride (3.0 mmol) in chloroform (5 mL) was added dropwise for 30 min. After stirring at 0°C−5°C for 2 h, the reaction mixture was warmed and stirred at 20°C for 18 h. Then the reaction mixture was filtered and the filtrate was washed with water (10 mL) and 5% potassium carbonate solution and dried over anhydrous sodium sulfate, and concentrated under diminished pressure. The products were purified by silica gel column chromatography with ethyl acetate-petroleum ether (V:V = 1:2) as the eluent, and then recrystallized in hexane to give **3a**−**3g**.

3 Results and discussion

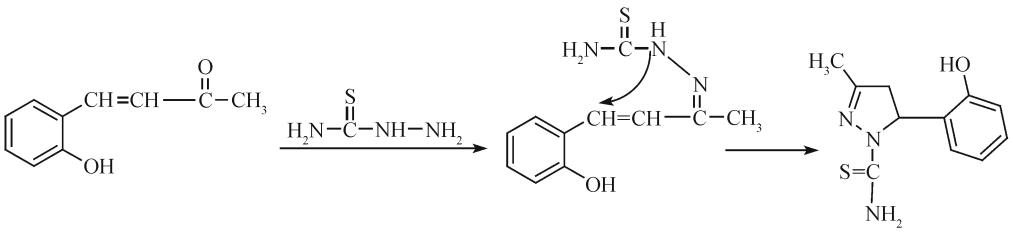
The data of physical constants, elemental analysis, ^{1}H NMR and IR of synthesized compounds are shown in Tables 1−3, respectively.

Table 1 Elemental analysis, mp, physical state and yield of compounds **2**, **3a**−**3g**

Compound	Physical state	Mp /°C	Yield /%	Elemental analysis		
				C	H	N
2	White solid	164−165	49.8	56.48 (56.17)	5.69 (5.53)	17.55 (17.87)
3a	White solid	128−130	56.7	58.01 (57.73)	6.03 (5.84)	14.78 (14.43)
3b	White solid	139−141	60.1	59.40 (59.02)	6.23 (6.23)	13.89 (13.77)
3c	White solid	127−128	50.4	60.90 (61.26)	6.99 (6.91)	13.01 (12.61)
3d	White solid	116−117	51.2	63.30 (63.16)	7.67 (7.48)	11.29 (11.63)
3e	White solid	140−141	52.9	64.00 (63.90)	7.65 (7.73)	10.88 (11.20)
3f	White solid	109−110	54.3	60.44 (60.45)	4.89 (4.79)	10.40 (10.58)
3g	White solid	143−144	60.3	50.47 (50.35)	3.91 (3.50)	17.27 (16.32)

Table 2 ^{1}H NMR data of compounds **2, 3a**−**3g**

Compound	^{1}H NMR (δ)
2	2.01 (s, 3H, Me), 2.77 (dd, 1H, J_1 = 18.4, J_2 = 3.3 Hz,4-Ha), 3.80 (dd, 1H, J_1 = 18.4, J_2 = 11.4 Hz,4-Hb), 5.24 (dd,1H, J_1 = 3.3, J_2 = 11.4 Hz, 5-H), 5.59 (s, 1H, —OH), 6.68−6.89 (m, 4H, ArH), 7.55−9.84 (br, 2H, NH_2)
3a	0.86 (t, 3H, —CH_3, J = 7.1Hz), 2.28−2.40 (m, 2H, $COCH_2$, 2.04 (s, 3H, Me)), 2.79 (dd, 1H, J_1 = 18.6, J_2 = 3.5Hz, 4-Ha), 3.80 (dd, 1H, J_1 = 18.6,J_2 = 11.7Hz, 4-Hb), 5.31 (dd, 1H, J_1 = 3.3, J_2 = 11.7 Hz, 5-H), 5.60 (s, 1H, -OH), 6.51−6.82 (m, 4H, ArH), 10.49 (s,1H,NH)
3b	0.88 (t,3H, —CH_3), 1.09−1.16 (m, 2H, —CH_2), 1.99 (s, 3H, Me), 2.28−2.36 (m, 2H, $COCH_2$), 2.84 (dd, 1H, 4-Ha), 3.81 (dd, 1H, 4-Hb), 5.40 (dd, 1H, 5-H), 5.66 (s, 1H, —OH), 6.54−6.90 (m, 4H, ArH), 10.60 (s, 1H, NH)
3c	0.88 (t, 3H, —CH_3), 1.11−1.20 (m, 6H, —$(CH_2)_3$), 1.99 (s, 3H, Me), 2.18−2.33 (m, 2H, $COCH_2$), 2.78 (dd, 1H, 4-Ha), 3.81 (dd, 1H, 4-Hb), 5.39 (dd, 1H, 5-H), 5.56 (s, 1H, —OH), 6.66−6.91 (m, 4H, ArH), 10.68 (s, 1H, NH)
3d	0.88 (t, 3H, —CH_3), 1.17−1.26 (m, 10H, —$(CH_2)_5$), 2.03 (s, 3H, Me), 2.18−2.35 (m, 2H, $COCH_2$), 2.80 (dd, 1H, 4-Ha), 3.67 (dd, 1H, 4-Hb), 5.35 (dd,1H, 5-H), 5.61 (s, 1H, —OH), 6.62−7.00 (m, 4H, ArH), 10.67 (s, 1H, NH)
3e	0.90 (t, 3H, —CH_3), 1.09−1.47 (m, 12H, -$(CH_2)_5$), 2.00 (s, 3H, Me), 2.16−2.29 (m, 2H, $COCH_2$), 2.80 (dd, 1H, 4-Ha), 3.69 (dd, 1H, 4-Hb), 5.40 (dd, 1H, 5-H), 5.69 (s, 1H, —OH), 6.68−7.14 (m, 4H, ArH), 10.74 (s, 1H, NH)
3f	1.06 (s, 3H, $OCOCH_3$), 2.01 (s, 3H, Me), 2.85 (dd, 1H, 4-Ha), 3.81 (dd, 1H, 4-Hb), 5.43 (dd, 1H, 5-H), 5.59 (s, 1H, -OH), 6.58−7.51 (m, 8H, ArH), 10.60 (s, 1H, NH)
3g	2.05 (s, 3H, Me), 2.82 (dd, 1H, 4-Ha), 3.77 (dd, 1H, 4-Hb), 5.34 (dd, 1H, 5-H), 5.63 (s, 1H, —OH), 6.56−8.38 (m, 7H, ArH), 11.09 (s, 1H, NH)



Scheme 2 Mechanism of condensation-addition

Table 3 IR data of compounds **2**, **3a**–**3g**

Compound	IR /(σ, cm^{-1})
2	3351.9 (—OH), 3247.4 (NH_2), 1270.8 (C=S), 1597.3 (C=N), 1447.1 ($—CH_3$).
3a	3403.0 (NH), 1271.8 (C=S), 1664.2 (C=O), 1427.0 ($—CH_2CO$), 1447.7 ($—CH_3$)
3b	3403.5 (NH), 1271.8 (C=S), 1664.5 (C=O), 1426.4 ($—CH_2CO$), 1447.3 ($—CH_3$)
3c	3402.6 (NH), 1272.3 (C=S), 1665.7 (C=O), 1426.4 ($—CH_2CO$), 1447.0 ($—CH_3$)
3d	3402.9 (NH), 1272.4 (C=S), 1665.4 (C=O), 1427.0 ($—CH_2CO$), 1446.8 ($—CH_3$)
3e	3402.4 (NH), 1271.8 (C=S), 1666.0 (C=O), 1426.7 ($—CH_2CO$), 1446.1 ($—CH_3$)
3f	3404.0 (NH), 1271.3 (C=S), 2938.1 (—Me), 1666.4 (C=O)
3g	3402.9 (NH), 1272.4 (C=S), 1767.7 (C=O), 995.1 (N-O)

We prepared the 3-methyl-pyrazole compound (compound **2**) from the reaction of α, β-unsaturated ketone with thiosemicarbazide. We suggested that condensation of the hydrazine with carbonyl occurred first to form hydrazone, then addition of the imino of hydrazone to the carbon-carbon double bond to afford the pyrazole derivative. Due to the electron withdrawing effect of the carbon-nitrogen double bond, α-carbon was more electron deficient compared to β carbon, and thus the nitrogen of imino attacked at the α-carbon as shown in Scheme 2 to form the five-membered pyrazole derivative **2** [20].

For acylation of the amino group of compound **2**, different bases, such as pyridine, triethylamine, sodium carbonate, potassium carbonate, and DMAP (*N,N*-dimethyl-4-aminopyridine) were tried. It was found that pyridine was the most effective one. In the reaction, pyridine not only adsorbed the released acid but also as catalyst, reacted with acyl chloride to form pyridinium salt generating acyl carbon ions [21].

The bactericidal activity against *E.coli* and *P.vulgaris* was measured by concentration dilution method. As shown in Table 4 ($mg \cdot L^{-1}$, minimum concentration for effective killing of the bacterium), compounds **3c**, **3d**, **3g** showed certain bactericidal activity against *E. coli* while compound **3g** showed certain bactericidal activity against *P. vulgaris*.

Table 4 Test result of bacterial activity/($mg \cdot L^{-1}$)

Compound	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
E.coli	–	–	250	250	–	–	500
P.vulgaris	–	–	–	–	–	–	500

–: no bacterial activity.

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