Front. Chem. China 2008, 3(4): 418–421
DOI 10.1007/s11458-008-0075-3

RESEARCH ARTICLE

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Synthesis and fungicidal activity of novel 3,5-diarylpyrazole derivatives

Abstract (*E*)-3-(2-chlorophenyl)-1-(2,4-dichlorophenyl) prop-2-en-1-one was prepared from 2-chlorobenzaldehyde followed by cyclization with hydrazine monohydrate. Eight new 3-(2,4-Di-chlorophenyl)-5-(2-chlorophenyl)-4,5- dihydro-*N*-acylpyrazole derivatives were synthesized and characterized by elemental analysis, IR and ^{1}H NMR spectroscopy. The experimental results show that the inhibition ratio of compounds 3f towards *H. Oryzae* and *P. oryzae* at 50 mg·L^{-1} is 55.2% and 57.1%, respectively. The inhibition ratio of compounds 3g towards *H. Oryzae*, *P. oryza*, *S. Sclerotiorum* at 50 mg·L^{-1} is 53.3%, 60.0%, 50.4% respectively.

Keywords 2-chlorobenzaldehyde, 3,5-diarylpyrazole, synthesis, fungicide

1 Introduction

The identification of the novel structures that can be potentially useful in designing new, potent antibacterial agents is still a major challenge to medicinal chemistry researchers. Many pyrazole derivatives are acknowledged to possess a wide range of bioactivities including antibacterial activity [1–6]. 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 3,5-diphenyl moiety. In our previous work, we reported that lots of 5-phenyl-pyrazole derivatives showed fungicidal activities [7–16]. Motivated by the aforementioned findings, we anticipate that the diaryl-4,5-dihydropyrazoles would exhibit antimicrobial activity. However, only a few reports have been dedicated to the synthesis and antimicrobial activities evaluation of diaryl-4,5-dihydropyrazoles. To extend our research on antibacterial compounds containing the diaryl-4,5-dihydropyrazole group, we designed a series of new diaryl-4,5-dihydropyrazole derivatives. In the molecular design of the diaryl-4,5-dihydropyrazoles, the rationale behind selecting a large number of compounds bearing different functionalities is to establish a definite structure-activity relationship pattern and emphasize the role of fluorine in imparting bioactivity. In this paper, (*E*)-3-(2-chlorophenyl)-1-(2,4-dichlorophenyl)prop-2-en-1-one was prepared from 2-chlorobenzal-dehyde followed by cyclization with hydrazine monohydrate (Scheme 1). Eight new 3-(2,4-Di-chlorophenyl)-5-(2-chlorophenyl)-4,5-dihydro-*N*-acylpyrazole derivatives were synthesized and characterized by elemental analysis, IR spectroscopy and ^{1}H-NMR spectroscopy.

2 Experimental

2.1 General

Melting points were measured uncorrected. The ^{1}H-NMR spectra were recorded on a Varian INOVA400 (400 MHz) pulse Fourier-transform NMR spectrometer in $CDCl_3$ or DMSO-d_6 using tetramethylsilane as an internal standard. Elemental analyses were performed by a Vario-III CHN analyzer and were within ±0.4% of the theoretical values. A Bruker Vector22 spectrometer was used to record IR spectra (KBr). The reagents were all either analytical or chemically pure grade.

2.2 (*E*)-3-(2-chlorophenyl)-1-(2,4-dichlorophenyl)prop-2-en-1-one (**1**)

To a three-necked 100 mL flask were added 1.41 g (10 mmol) 2-chlorobenzaldehyde, 1.90 g (10 mmol) 1-

Translated from *Chinese Journal of Applied Chemistry*, 2007, 27(7): 835–837

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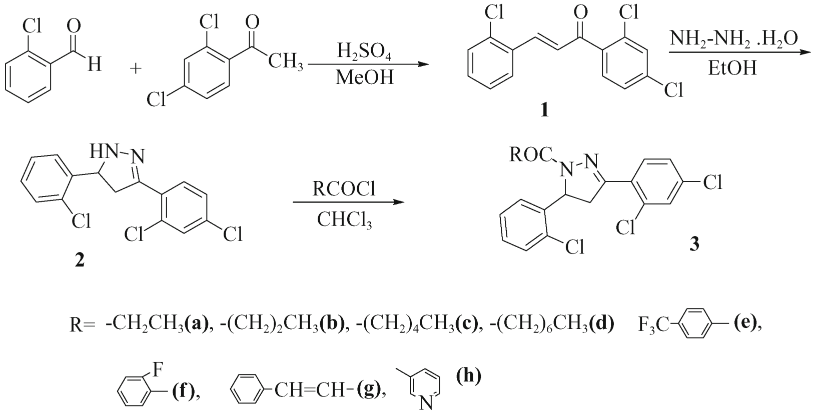

Scheme 1 Synthesis route of 3, 5-diarylpyrazole derivatives

(2,4-dichlorophenyl)ethanone, 30 mL methanol and catalytic H_2SO_4. The mixture was heated under reflux for 5 h and then kept at 0°C for 10 h. The reaction mixture was filtered to obtain a yellow solid. The solid was washed with ice water and then recrystallized in ethanol to give a colorless solid (1.44 g) with a yield of 46.2%.

2.3 5-(2-chlorophenyl)-3-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazole (2)

To a three-necked 100 mL flask were added 2.12 g (10 mmol) α, β-unsaturated ketone **1**, 0.50 g (10 mmol) hydrazine, and 30 mL ethanol. The mixture was heated under reflux for 4 h. The reaction was monitored by thin layer chromatography (TLC) (V(acetone): V(petroleum ether 60°C–90°C) = 1:1) and stopped when the TLC showed only one spot with $R_f = 0.45$. The reaction mixture was filtered to give a pale yellow solid. The solid was recrystallized in DMF to give **2** as a colorless solid (2.0 g) with a mp of 207–208. The yield was 61.4%.

2.4 1-(5-(2-chlorophenyl)-3-(2,4-dichlorophenyl)-4,5-dihydropyrazol-1-yl)-one

In a 50 mL three-necked round-bottom flask, 0.82 g (2.0 mmol) compound **2** was mixed with pyridine (2.0 mL) and then dry chloroform (30 mmol) was added. The resulting solution was stirred and cooled to 0°C–5°C in an ice bath. A solution of chloride (4.0 mmol) in chloroform (10 mL) was added dropwise for 30 min. After stirring at 0°C–5°C for 2 h. Then the reaction mixture was filtered and the filtrate was washed with water (10 mL) and 5% potassium carbonate solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The products were purified by silica gel (0.074–0.049 mm) column chromatography with ketone-petroleum ether (V: V = 1:3) as the eluent, and then recrystallized in ethyl acetate-petroleum ether (V: V = 1:3) to give **3a–3h**.

3 Results and discussion

3.1 The physical constants and the results of the elemental analysis, ^{1}H-NMR spectroscopy and IR spectroscopy of the synthesized compounds are shown in Tables 1–3, respectively.

3.2 The synthesis of compound 2

Hydrazine, a compound where two nitrogen atoms are directly linked through σ bonds, is a weak base. This functional group is nucleophilic in nature. The nitrogen

Table 1 Elemental analysis, mp, physical state and yield of compounds **2**; **3a–3h**

					elemental analysis, Anal. Found (calcd)/%		
Compound	appearance	m.p/(°C)	Formula	yield/%	C	H	N
2	white solid	207–208	$C_{15}H_{11}Cl_3N_2$	61.2	55.49 (55.33)	3.57 (3.40)	8.38 (8.60)
3a	white solid	189–191	$C_{18}H_{15}Cl_3N_2O$	54.2	56.92 (56.64)	4.12 (3.96)	7.60 (7.34)
3b	white solid	179–180	$C_{19}H_{17}Cl_3N_2O$	50.5	58.03 (57.67)	4.20 (4.33)	7.22 (7.08)
3c	white solid	186–187	$C_{21}H_{21}Cl_3N_2O$	51.8	59.77 (59.52)	5.20 (4.99)	6.44 (6.61)
3d	white solid	191–192	$C_{23}H_{25}Cl_3N_2O$	49.2	61.00 (61.14)	5.69 (5.58)	5.98 (6.20)
3e	white solid	144–146	$C_{23}H_{14}Cl_3F_3N_2O$	48.7	55.37 (55.50)	3.01 (2.84)	5.71 (5.63)
3f	white solid	211–213	$C_{22}H_{14}Cl_3FN_2O$	52.2	58.78(59.02)	2.97 (3.15)	6.51 (6.26)
3g	white solid	201–202	$C_{24}H_{17}Cl_3N_2O$	40.8	63.19 (63.25)	3.74 (3.76)	6.28 (6.15)
3h	white solid	218–219	$C_{21}H_{14}Cl_3N_3O$	55.4	58.54 (58.56)	3.29 (3.28)	10.00 (9.76)

Table 2 IR data of compounds **2; 3a–3h**

compound	IR, σ/cm^{-1}
2	3443.6(NH),2929.0(CH_3),1631.4(C=N),1104.9(C–N)
3a	1644.4(C=O), 1629.8 (C=N), 2928.9(CH_3), 1420.8(–CH_2CO)
3b	1643.9(C=O), 1628.9(C=N), 2928.2(CH_3) , 1420.6(–CH_2CO)
3c	1643.5(C=O), 1628.9(C=N), 2929.0(CH_3) , 1420.8(–CH_2CO)
3d	1643.2(C=O), 1629.0(C=N), 2928.8(CH_3) , 1421.0(–CH_2CO)
3e	1696.4(C=O), 1629.3(C=N), 2928.9(CH_3), 1441.4(–CH_3)
3f	1700.9(C=O), 1629.6 (C=N), 2928.8(CH_3),1442.1(–CH_3)
3g	1674.8(C=O), 1630.2 (C=N), 2929.4(CH_3),1442.7(–CH_3)
3h	1708.9(C=O), 1629.9(C=N), 2928.8(CH_3),1442.4(–CH_3) , 3044.0(Py-)

Table 3 ^{1}H-NMR data of compounds **2; 3a–3h**

compound	^{1}H-NMR ,δ
2	3.09 (dd, 1H, $J_1 = 10.4$, $J_2 = 16.1$Hz, 4-Ha), 3.57 (dd, 1H, $J_1 = 10.5$, $J_2 = 16.1$Hz, 4-Hb), 5.37 (dd,1H, $J_1 = 3.6$, $J_2 = 10.3$ Hz, 5-H), 6.18 (brs, 1H, NH),7.04–7.51 (m, 7H, ArH)
3a	0.89 (t, 3H, -CH_3, $J = 7.2$Hz), 2.52–2.73 (m, 2H, $COCH_2$), 3.10 (dd, 1H, $J_1 = 10.5$, $J_2 = 16.4$Hz, 4-Ha), 3.60 (dd, 1H, $J_1 = 10.5$, $J_2 = 16.0$Hz, 4-Hb), 5.39 (dd, 1H, $J_1 = 3.6$, $J_2 = 10.2$ Hz, 5-H), 7.02–7.50 (m, 7H, ArH)
3b	0.88 (t, 3H, -CH_3, $J = 7.2$Hz), 1.21–1.29 (m, 2H, -CH_2), 2.58–2.67 (m, 2H, $COCH_2$), 3.09 (dd, 1H, $J_1 = 10.5$ $J_2 = 16.3$Hz, 4-Ha), 3.59 (dd, 1H, $J_1 = 10.5$, $J_2 = 16.1$Hz, 4-Hb), 5.38 (dd, 1H, $J_1 = 3.6$, $J_2 = 10.1$ Hz, 5-H), 7.04–7.52 (m, 7H, ArH)
3c	0.87 (t, 3H, -CH_3, $J = 7.2$Hz), 1.34–1.42 (m, 6H, -3CH_2), 2.57–2.66 (m, 2H, $COCH_2$), 3.09 (dd, 1H, $J_1 = 10.5$ $J_2 = 16.4$Hz, 4-Ha),3.58 (dd, 1H, $J_1 = 10.5$, $J_2 = 16.0$Hz, 4-Hb), 5.40 (dd, 1H, $J_1 = 3.6$, $J_2 = 10.0$ Hz, 5-H), 7.02–7.49 (m, 7H, ArH)
3d	0.87 (t, 3H, -CH_3, $J = 7.2$Hz), 1.38–1.47 (m, 10H, -5CH_2), 2.51–2.68 (m, 2H, $COCH_2$), 3.06 (dd, 1H, $J_1 = 10.5$, $J_2 = 16.4$Hz, 4-Ha), 3.55 (dd, 1H, $J_1 = 10.6$, $J_2 = 16.1$Hz, 4-Hb), 5.32 (dd, 1H, $J_1 = 3.7$, $J_2 = 10.2$ Hz, 5-H), 7.05–7.51 (m, 7H, ArH)
3e	3.04 (dd, 1H, $J_1 = 10.6$, $J_2 = 16.4$Hz, 4-Ha), 3.52 (dd, 1H, $J_1 = 10.5$, $J_2 = 16.2$Hz, 4-Hb), 5.34 (dd, 1H, $J_1 = 3.7$, $J_2 = 10.2$ Hz, 5-H), 7.02–7.48 (m, 7H, ArH), 7.62–7.83 (m, 4H, CF_3-ArH)
3f	3.06 (dd, 1H, $J_1 = 10.5$, $J_2 = 16.4$Hz, 4-Ha), 3.52 (dd, 1H, $J_1 = 10.5$, $J_2 = 16.1$Hz, 4-Hb), 5.36 (dd, 1H, $J_1 = 3.6$, $J_2 = 10.2$ Hz, 5-H), 7.01–7.93 (m, 11H, ArH)
3g	3.08 (dd, 1H, $J_1 = 10.5$, $J_2 = 16.3$Hz, 4-Ha), 3.55 (dd, 1H, $J_1 = 10.5$, $J_2 = 16.1$Hz, 4-Hb), 5.34 (dd, 1H, $J_1 = 3.6$, $J_2 = 10.1$ Hz, 5-H), 6.88 (d, 1H, -CH=), 7.00–7.54 (m, 12H, ArH), 7.58 (d, 1H, =CHCO-)
3h	3.10 (dd, 1H, $J_1 = 10.4$, $J_2 = 16.2$Hz, 4-Ha), 3.56 (dd, 1H, $J_1 = 10.4$, $J_2 = 16.1$ Hz, 4-Hb), 5.36 (dd, 1H, $J_1 = 3.6$, $J_2 = 10.1$ Hz, 5-H), 7.02–7.53 (m, 7H, ArH), 7.59–9.18 (m, 4H, Py-H)

Table 4 Inhibition ratio of compounds **3** towards fungi at 50 mg·L^{-1}

compound	Inhibition ratio/%			compound	Inhibition ratio/%		
	H. oryzae	*P. oryzae*	*S. sclerotiorum*		*H. Oryzae*	*P. oryzae*	*S. Sclerotiorum*
3a	18.9	12.1	4.6	**3e**	46.5	39.2	2.8
3b	40.1	39.8	25.2	**3f**	55.2	57.1	24.2
3c	21.2	9.9	40.2	**3g**	52.3	60.0	50.4
3d	14.7	23.2	37.3	**3h**	49.2	38.2	20.0

in hydrazine improves the phenomenon known as the α_2 effect. This α_2 effect may be due to the reaction of hydrazine, as a nucleophile, with the reagent. The nitrogen-nitrogen bond lends electronic stability to the transition state.

3.3 The bactericidal activity of the compounds

The bactericidal activity against *H. oryzae*, *P. oryza*, *S. sclerotiorum* was measured by the series dilution method. As shown in Table 4, compound **3f** showed bactericidal activity against *H. oryzae*; compound **3g** showed certain bactericidal activity against *H. Oryzae*, *P. oryza*, *S. Sclerotiorum.* There is no significant difference in the bactericidal activity shown by the compounds with the introduction of the **F** group. The compounds synthesized in this study are relatively few and have a narrow range. We are unable to distinguish the compounds with truly high activity. Further studies on the design and synthesis of such compounds would be worthwhile.

Acknowledgements The project was supported by the Young College Teachers Research Projects of Anhui Province (2005JQ1075) and Universities Natural Science Research Projects of Anhui Province (2006KJ104B)

References

1. Tanitame A, Oyamada Y, Ofuji K, Kyoya Y, Suzuki K, Ito H, Kawasaki M, Nagai K, Wachid M, Yamagishi J I. Design, synthesis and structure–activity relationship studies of novel

indazole analogues as DNA gyrase inhibitors with Gram-positive antibacterial activity. Bioorg Med Chem Lett, 2004, 14: 2857–2862

2. Bekhita A A, Abdel-Aziem T, Design, synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatory-antimicrobial agents. Bioorg Med Chem, 2004, 12: 1935–1945
3. Lee C S, Allwine D A, Barbachyn M R, Grega K C, Dolak L A, Ford C W, Jensen R M, Seest E P, Hamel J C, Schaadt R D, Stapert D, Yagi B H, Zurenkoc G E, Genina M J, Carbon–carbon-linked (pyrazolylphenyl) oxazolidinones with antibacterial activity against multiple drug resistant gram-positive and fastidious gram-negative bacteria. Bioorg Med Chem, 2001, 9: 3243–3252
4. Tanitame A, Oyamada Y, Ofuji K, Fujimoto M, Suzuki K, Ueda T, Terauchi H, Kawasaki M, Nagai K, Wachie M, Yamagishib J I. Synthesis and antibacterial activity of novel and potent DNA gyrase inhibitors with azole ring. Bioorg Med Chem, 2004, 12: 5515–5524
5. Boyer F E, Vara Prasad J V N, Choy A L, Chupak L, Dermyer M R, Synthesis and SAR of novel conformationally-restricted oxazolidinones possessing Gram-positive and fastidious Gram-negative antibacterial activity. Part 1: Substituted pyrazoles. Bioorg Med Chem Lett, 2007, 17: 4694–4701
6. Tanitame A, Oyamada Y, Ofuji K, Terauchi H, Kawasaki M, Wachic M Yamagishi J, Synthesis and antibacterial activity of a novel series of DNA gyrase inhibitors: 5-[(E)-2-arylvinyl] pyrazoles. Bioorg Med Chem Lett, 2005, 15: 4299–4306
7. Liu X H, Pin C, Song B A, Pinaki S B, Zhu H L, wang S F, Novel 1-(5-substituted-3-substituted-4,5-dihydropyrazol-1-yl) ethanone oxime ester derivatives:synthesis, structure and antibacterial activity. Bioorg Med Chem Lett, 2008, 16: 4075–4082
8. Liu X H, Li B, ZhuH L, Song B A. Novel 5-aryl pyrazole derivatives: synthesis, structure, and antibacterial activity. Austra J Chem, 2008, 61: 223–230
9. Liu X H, Song B A, Zhu H L, Zuo R B, Synthesis, characterization andantibacterial activity of new 3, 5-diaryl pyrazole oxime ester derivatives. Chin J Chem, 2008, 26: 505–509
10. Liu X H, Zhi L P, Song B A. Novel 5-aryl pyrazole oxime ester derivatives: synthesis, structure and antibacterial activity. Chem Res Chinese U, 2008, 24(4): DOI: 1005-9040 (2008)-03-001-07
11. Liu X H, Wang S F, Song B A. Synthesis and bactericidal activities of novel pyrazole-1-carbothioamide derivatives. Front Chem China, 2007, 2(3): 311–314
12. Liu X H, Bai L S, Wang S F. Synthesis and antibacterial activity of 5-(2-hydroxyphenyl)-3-methyl aminopyrazole. Chin J Synth Chem, 2006, 14(2): 147–149 (in Chinese)
13. Liu X H, Bau L S, Wang S F. Synthesis of 5-(2- hydroxy-6-methoxylphenyl)-3-methyl-4, 5-dihydropyrazole-1-carbothioamide derivatives. Chin J Synth Chem, 2006, 14(3): 272–274 (in Chinese)
14. Liu X H. Synthesis and fungicide activity of novel arylpyrazole derivatives. Chin J Synth Chem, 2007, 15(2): 212–215 (in Chinese)
15. Liu X H, Zhu J, Pan C X, Song B A. Synthesis and fungicide activity of novel 5-arylpyrazole derivatives. Chin J Appl Chem, 2007, 24(10): 1162–1166 (in Chinese)
16. Liu X H. Synthesis and characterize of 5-(2-hydroxy-6-methoxylphenyl)-3-methyl aminopyrazole. J Anhui Univ Technol, 2006, 23(3): 275–277 (in Chinese)