SYNTHESIS OF 5-CHLORO-3-METHYL-1 PHENYL-1H PYRAZOLE-4-CARBOXYLIC ACID HETEROCYCLIC- 2-YLAMIDE

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Abstract: Reaction of 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbonyl chloride **4** with substituted benzothiazol-2-ylamine and substituted [1,3,4] thiadiazol-2-ylamine yields 5-chloro-3-methyl-1-phenyl-1H pyrazole-4-carboxylic acid-substituted benzothiazol-2-ylamide **5** and 5-chloro-3-methyl-1-phenyl-1H pyrazole-4-carboxylic acid (5-substituted -[1,3,4] thiadiazol-2-yl)amide **6** respectively in good yields.

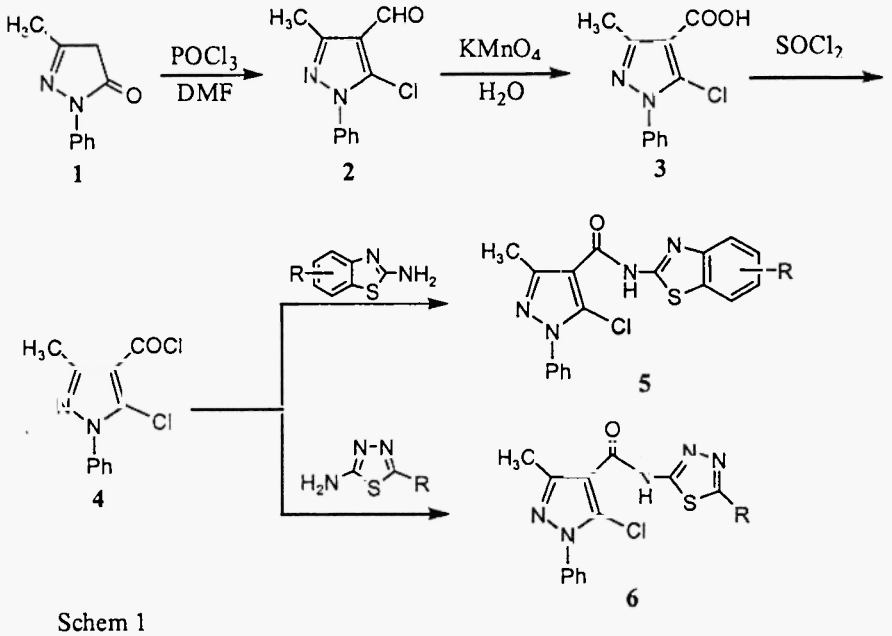
Introduction

A number of biologically interesting azo-heterocylic compounds have received considerable attention since the play an important role in the prevention of various plant diseases. Such as, they can be used as pesticide, acaricide, herbicide and fungicide[1-3]. Therefore, development of novel azo-heterocyclic compounds is of great interest to both heterocylic studies and pesticide application. In continuation of our previous studies in the synthesis of biologically active heterocyclic compounds[4-7], we have synthesized the hitherto unreported synthesis of 5-chloro-3-methyl-1-phenyl-1H pyrazole-4-carboxylic acid heterocyclic-2-ylamide **5** and **6** from 5-methyl-2-phenyl-2,4-dihydro-pyrazol-3-one **1**.

Results and Discussion

5-methyl-2-phenyl-2,4-dihydro-pyrazol-3-one **1** with phosphorus oxychloride was heated under reflux to give expected 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde **2** as pale yellow crystal, which was oxidated by potassium permanganate in water to result in 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid **3** as white power, subsequently, compound **3** was chloridized by sulfuric chloride to form 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbonyl chloride 4, which reacted with 5-alkyl-2,5-dihydro- [1,3,4]thiadiazole-2-ylamine or substituted benzothiazol-2-ylamine in mixture of chloroform, triethylamine and DMSO under reflux for 4-6 hours to give title compounds **5** and **6**, as depicted in scheme 1.

The structure of the title compounds has been confirmed by analytical results and spectral data IR, ^{1}H NMR, MS. The ^{1}H NMR spectrum of all these compounds (**5** and **6**) displayed a sharp singlet at δ about 2.5 ppm, which is characteristic for C_3-CH_3 of pyrazole moiety. The IR spectra showed peaks at about 1700cm^{-1}($\upsilon_{C=O}$) and about 3390 cm^{-1}(υ_{N-H}). The EI-MS spectra showed the existence of weak molecular ion peak, the fragment ion peaks were consistent with their structures. Taken compound **5a** as representative example, which gave correct elemental analysis, in IR spectra showed peak at 3390 cm^{-1}(υ_{N-H}) and 1707 cm^{-1}($\upsilon_{C=O}$), and 1590 cm^{-1}, 1506 cm^{-1}, 1435 cm^{-1} for aromatic ring. ^{1}H NMR spectrum displayed a sharp singlet at δ2.40 ppm for C_3-CH_3 , a multiplet at 7.22-7.45ppm for aromatic protons and a wide peak at 10.43ppm for NH. The EI-MS spectra showed the existence of M^+ peak, the fragment ion peaks m/z are 333, 236, 219, 221, 155, 150 and 77.



Schem 1

5a R=H, **5b** R=4-Cl, **5c** R=6-CH_3, **5d**=4-CH_3
6a R=H, **6b** R=CH_3, **6c** R=C_2H_5, **6d**=i-C_3H_7, **6e** R=CF_3

Experimental

Melting points were determined in open glass capillaries on a Electrothermal digital melting apparatus and melting point apparatus are uncorrected.^{1}H NMR spectra were recorded on VARIANN XL 200 spectrometers (chemical shifts in δ ppm using TMS as internal standard, $CDCl_3$ or DMSO-d_6 as solvent) and IR spectra were recorded in KBr on a NICOLET AVATAR 360 spectrum apparatus. Mass Spectra were recorded on FINNGAM TRACE MS spectrometer, elemental analyses were carried out on a MT-3 analyzer.

Preparation of 5-chloro-3-methyl-1-phenyl-1H pyrazole-4-carboxylic acid heterocyclic-2-ylamide (5)

To substituted benzothiazol-2-ylamine (6.5mmol) and triethylamine (6.5mmol) was added the mixed solvent of 20mL chloroform and 3mL DMSO, then, 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbonyl chloride **4** (6mmol) dissolved in 10mL chloroform was added dropwise to above mixture at 10℃, subsequently, the mixture was refluxed 4-6 hours, then the solution was washed by 10% hydrochloric acid, water and brine in turn. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The products were purified by recrystalliza- tion in ethanol.

5a: offwhite powder, mp 175-178℃; Yield 65.3%; ^{1}H NMR (δ,ppm) 2.40(s,3H,CH_3), 7.22-7.45(m,9H,Ar-H), 10.43(s,1H,NH); IR (cm^{-1}) 3390(ν_{NH}), 1707 ($\nu_{C=O}$); EI-MS m/z(%): 368(M+,2.8), 333(37.1), 219(100), 221(49. 9), 150(14.79),77(39.5); found: C,58.49; H,3.60; N,15.32; Calcd for $C_{18}H_{13}ClN_4OS$: C,58.61; H,3.55; N,15.19

5b: yellow powder, mp 184-186℃; Yield 70.0%; ^{1}H NMR (δ,ppm) 2.43(s,3H,CH_3), 7.54-7.68(m,8H,Ar-H), 10.58(s,1H,NH); IR (cm^{-1}) 3392(ν_{NH}), 1710($\nu_{C=O}$); found: C,53.41; H, 3.06; N, 14.08; Calcd for $C_{18}H_{12}Cl_2N_4OS$: C, 53.60; H,3.00; N, 13.89

5c: orange needle crystal, mp 163-165℃; Yield 68.4%; ^{1}H NMR (δ,ppm) 2.41(s,3H,CH_3), 2.44(s,3H,CH_3), 7.50-7.75(m,8H,Ar-H), 10.38(s,1H,NH); IR (cm^{-1}) 3395(ν_{NH}), 1702($\nu_{C=O}$); found: C, 59.48; H, 4.04; N, 14.71; Calcd for $C_{19}H_{15}ClN_4OS$: C, 59.60; H, 3.95; N, 14.63

5d: yellow crystal, mp 200-201℃; Yield 75.1%; ^{1}H NMR (δ,ppm) 2.61(s,3H,CH_3), 2.64(s,3H,CH_3), 7.48-7.66(m,8H,Ar-H), 10.00(s,1H,NH); IR (cm^{-1}) 3393(ν_{NH}), 1705($\nu_{C=O}$); found: C, 59.40; H, 3.94; N, 14.67; Calcd for $C_{19}H_{15}ClN_4OS$: C, 59.60; H, 3.95; N, 14.63

Preparation of 5-chloro-3-methyl-1-phenyl-1H pyrazole-4-carboxylic acid (5-substituted-[1,3,4]thiadiazol-2- yl)amide (6)

To a stirred solution of 6.5mmol of substituted [1,3,4] thiadiazol-2-ylamine and 6.5mmol of triethylamine in 20mL of chloroform, a mixture of 6mmol of 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbonyl chloride **4** and 10mL of chloroform was added dropwise at 10℃, then, the mixture was refluxed 4-6 hours, after cooling to room temperature, the solution was washed by 10% hydrochloric acid, water and brine in turn. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The products were purified by recrystallization in ethanol.

6a: white crystal, mp 204-205℃; Yield 67.9%; ^{1}H NMR (δ,ppm) 2.55(s,3H,CH_3), 7.35-7.63(m,5H,Ar-H), 8.80(s,1H,Het-H), 10.07(s,1H,NH); IR (cm^{-1}) 3418(ν_{NH}), 1662 ($\nu_{C=O}$); EI-MS m/z(%): 319(M+,1.6), 284(8.7), 221(7.4), 219(21.4), 150(3.4), 104(15.6), 77(100); found: C,48.68; H,3.29; N,21.85; Calcd for $C_{13}H_{10}ClN_5OS$: C,48.83; H,3.15; N,21.91

6b: white crystal, mp 198-199℃; Yield 79.4%; ^{1}H NMR (δ,ppm) 2.55(s,3H,CH_3), 2.60(s,3H,CH_3), 7.34-7.58(m,5H,Ar-H); IR (cm^{-1}) 34152(ν_{NH}), 1665($\nu_{C=O}$); EI-MS m/z(%): 333(M+,1.3), 298(18.8), 221(18.5), 219(58.5), 150(11.1), 104(15.6), 77(100); found: C,50.32; H,3.75; N,20.94; Calcd for $C_{14}H_{12}ClN_5OS$: C,50.37; H,3.62; N,20.99

6c: yellow crystal, mp 148-150℃; Yield 69.4%; ^{1}H NMR (δ,ppm) 1.37-1.44(t,3H,CH_3), 2.59(s,3H,CH_3), 2.99-3.11(m,2H,CH_2), 7.46-7.55(m,5H,Ar-H), 10.50(s,1H,NH); IR (cm^{-1}) 3434(ν_{NH}), 1658 ($\nu_{C=O}$); found: C,51.65; H,4.35; N,20.19; Calcd for $C_{15}H_{14}ClN_5OS$: C,51.79; H,4.06; N,20.14

6d: white crystal, mp 131-132℃; Yield 78.6%; ^{1}H NMR (δ,ppm) 1.39-1.42(d,6H,CH_3), 2.57(s,3H,CH_3), 3.32-3.39(m,1H,CH), 7.45-7.52(m,5H,Ar-H); IR (cm^{-1}) 3425(ν_{NH}), 1660($\nu_{C=O}$); found: C,53.01; H,4.58; N, 19.24 Calcd for $C_{16}H_{16}ClN_5OS$: C,53.11; H,4.46; N,19.35

6e: white needle crystal, mp 145-146℃; Yield 71.3%; ^{1}H NMR (δ,ppm) 0.90-0.97(t,3H,CH_3), 1.36-1.47(m,2H,CH_2), 1.68-1.79(m,2H,CH_2), 2.57(s,3H,CH_3), 2.96-3.04(t,2H,CH_2), 7.44-7.56(m, 5H,Ar-H), 11.00(s,1H,NH); IR (cm^{-1}) 3430(ν_{NH}), 1659 ($\nu_{C=O}$); EI-MS m/z(%): 375(M+,0.3), 340(18.8), 221(35.5), 219(100), 155(10.3), 104(7.6), 77(29.9); found: C, 54.41; H, 4.99; N, 18.68; Calcd for $C_{17}H_{18}ClN_5OS$: C, 54.32; H, 4.83; N, 18.63

6d: white crystal, mp 215-216℃; Yield 80.7%; ^{1}H NMR (δ,ppm) 2.40(s,3H,CH_3), 7.50-7.54(m,5H,Ar-H), 9.70(s,1H,NH); IR (cm^{-1}) 3440(ν_{NH}), 1663($\nu_{C=O}$); EI-MS m/z(%): 275(8.7), 235(5.3), 219(27.8), 155(2.1), 77(45.0), 40(100); found: C, 43.25; H, 2.38; N, 17.98; Calcd for $C_{14}H_9ClF_3N_5OS$: C, 43.36; H2.34; N, 18.06

References

1. W.G. Zhao, Z.m. Li, P.W. Yuan, Chinese Journal of Organic Chemistry, **21**(8), 593 (2001)
2. S.Hitoshi, I.Tutomu, Y.Hideo, US patent US 4792565 (1988)
3. H.Walter, World Patent WO142223 (2001)

4. Liming Hu, Zhaojie Liu, Hansheng Xu, *Journal of Tsinghua University (Science and Technology)*, **41** (S1) ,67 (2001)
5. L.M. Hu, H.S. Xu, Z.J.Liu, *Phosphorus, Sulfur and Silicon*, **2002**, 177(12), 2785-2790
6. L.M. Hu, W.X.Lei, J.H.Feng, *Journal of Central China Normal University (Science and Technology)* 36(2),204(2002)
7. L.M Hu, H.S.Xu , Z.J. Liu, *Phosphorus, Sulfur and Silicon*, 163,211 (2000)

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