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Synthesis of Some Pyridazine Based Pyrazolines

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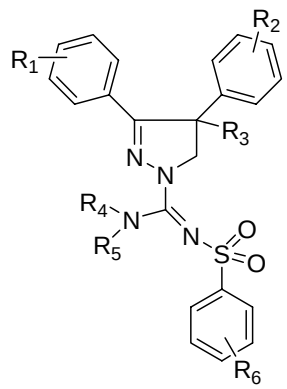
3-Chloro-6-hydrazinyl pyridazine reacts with chalcones to give 1,3,5-trisubstituted pyrazolines. Some of these display reasonable antibacterial activity.

Keywords: Hydrazinylpyridazine, Mass spectra, Synthesis.

INTRODUCTION

Pyrazolines are reduced pyrazoles and thus form an important class of organic compounds with interesting chemical and biological properties. Pyrazolines can be either obtained by partial reduction of a pyrazole or can be independently synthesized from acyclic material [1]. A recent review deals with synthetic and biological aspects of pyrazolines [2]. Many uses of pyrazolines include their antidepressant and anticonvulsant [3], antibacterial [4], anti-inflammatory [5] and as potent and selective CB_1 cannabinoid receptor antagonists (**1**) [6]. We had earlier reported synthesis and biological screening of various derivatives of pyrazolylpyridazines [7]. Having access to the pyridylhydrazine we attempted to prepare some of its diaryl pyrazoline derivatives, which are now being communicated.



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EXPERIMENTAL

All the starting and other compounds and reagents were obtained from Merck or Fluka Chemicals. These were of reagent grades and were used without further purification, however when required these were purified by standard methods. Melting points were determined on a Gallenkamp apparatus and are uncorrected. FTIR spectra were recorded on a Hitachi FTIR 4300 or Thermo Nicolet FTIR-200 spectrometer. NMR spectra (^{1}H and ^{13}C) were taken on a Bruker AVANCE 300-600 MHz and in solvents DMSO-d_6 or $CDCl_3$. Chemical shifts are reported in ppm relative to tetramethylsilane an internal standard. Mass spectra were taken either on Jeol JMS-HX110H or on Agilent GC-MS spectrophotometer 5890. Elemental analysis (C, H, N) was carried out on Elementar Vario MACRO CHNS analyzer. Progress of all the reactions was monitored by thin layer chromatography (TLC), which was performed on aluminium sheets, precoated with silica gel (Merck, Kiselgel 60 F-254) (0.2 mm). Column chromatography, when required was carried out using E. Merck silica gel type 60 (70-230 mesh) and aluminium oxide basic (Panreac). Spots were checked under UVGL-25 Mineral light multi-band UV-254/366 nm lamp. Some plates were observed in iodine vapours. The antibacterial screening was conducted by following the disk protocol [8].

Chalcones (2-6): The following chalcones (**2-6**) were prepared according to the standard procedures [9]: 1,3-diphenyl prop-2-en-1-one (**2**) m.p.: 52-54 °C, 1-phenyl pent-1-en-3-one (**3**) m.p.: 55-57 °C, 1-(4-hydroxyphenyl)-3-phenyl-prop-2-en-1-one (**4**) m.p.: 148-150 °C, 3-(4-chlorophenyl)-1-

phenylprop-2-en-1-one (**5**) m.p.: 110-114 °C, 3-(4-nitorophenyl)-1-phenylprop-2-en-1-one (**6**) m.p.: 155-157 °C.

Pyrazolines (7-11)

Method A: An equimolar quantity (3.46 mmol) of 3-chloro-6-hydrazinylpyridazine [7] (0.5 g), an appropriate chalcone (**2-6**) (0.72 g) and 10 mL ethanol was heated under reflux for 6 h. The reaction mixture was cooled and diluted with 20 mL water, the precipiate formed were filtered, dried at room temperature and was purified by column chromatography on basic aluminium oxide, using benzene as an eluent.

Method B: The mixture of reactants was heated under reflux in toluene for 6 h. the same product was obtained as in method A.

Method C: The mixture of reactants was heated under reflux in ethanol in the presence of 1 mL piperidine for 6 h.

The best results were obtained from method C, hence the rest of the reactions of 3-chloro-6-hydrazinyl pyridazine and other chalcones were performed following this method.

3-Chloro-6-(3,5-diphenyl-2,3-dihydro-1*H*-pyrazol-1-yl)pyridazine (7): It was obtained from the reaction of an equimolar quantities (3.46 mmol) of 3-chloro-6-hydrazinylpyridazine (0.5 g), (**2**) (0.55 g) and piperidine 1 mL in 10 mL ethanol.

Yield: 0.70 g (60 %); m.p.: 188-190 °C; IR (KBr, ν_{max}, cm^{-1}): 1617, 1584, 3058, 2999, 2920 &1445. MS *m/z* % 332 [M^+, 100] 334 [33 %]; Elemental analysis for $C_{19}H_{13}N_4Cl$: Calculated: C, 68.57; H, 3.94; N, 16.84. Found: C, 68.28; H, 3.92; N, 16.20 %; ^{1}H NMR (DMSO-d_6): δ: 5.9 (s, 2H, 4-H pyrazole), 7.24-7.34 (m, 5H, 2,3,4,5,6-H 3-phenylpyrazole), 7.51 (d, *J* = 9.0 Hz, 1H, 4-H pyridazine), 7.60 (d, *J* = 9.0 Hz, 1H, 5-H pyridazine), 7.69 (m, 5H, 5-phenyl pyrazole).

Method B: Yield 16 %; **Method C:** Yield 60 %.

3-Chloro-6-(3-ethyl-5-phenyl-2,3-dihdro-1*H*-pyrazol-1-yl)pyridazine (8): It was obtained from the reaction of an equimolar quantities (3.46 mmol) of 3-chloro-6-hydrazinylpyridazine, 1-phenylpent-1-en-3-one (**3**) (0.55 g) and piperidine 1 mL in 10 mL ethanol. Yield: 0.5 g (51 %); m.p.: 102-104 °C; IR (KBr, ν_{max}, cm^{-1}):1611, 1495, 1382, 1478, 3023, 2966, 2926, 1581 and 1565. MS *m/z* %: 286 [M^+, 100], 288 [M^+, 33].

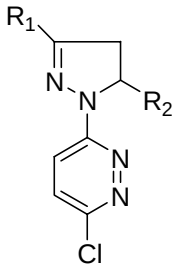
4-[1-(6-Chloropyridazin-3-yl)-5-phenyl-2,3-dihydro-1*H*-pyrazol-3-yl]phenol (9): It was obtained from the reaction of an equimolar quantities (3.46 mmol) of 3-chloro-6-hydrazinylpyridazine (0.5 g), 1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one (**4**) (0.76 g) and piperidine 1.0 mL in 10 mL ethanol. Yield: 0.6 g (49.58 %); m.p.: 150-155 °C; IR (KBr, ν_{max}, cm^{-1}): 3297, 1611, 1495, 3276 (-OH str.) 2945, 2889 and 1424.; MS *m/z* %:252 [M^+, 100], 254 [M^+ 33].

3-Chloro-6-[5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]pyridazine (10): It was obtained from the reaction of an equimolar quantities (3.46 mmol) of 3-chloro-6-hydrazinylpyridazine (0.5 g), 3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (**5**) (0.83 g) and piperidine 1 mL in 10 mL ethanol. Yield: 1.0 g (78 %); m.p.: 173-175 °C; IR (KBr, ν_{max}, cm^{-1}), 1624, 1463, 3054, 2999, 2935, 1582,1565 and 1443.MS *m/z* 370 [M^+,100], 371 [M^+ 33], 372 [M^+ 22]. ^{1}H NMR ($CDCl_3$) δ: 7.26 (s, 1H, 5-H pyrazole), 7.28 (d, *J* = 4.2 Hz, 2H, 4-H pyrazole), 7.39-7.49 (m, 5H, 3-phenyl), 7.51 (d, *J* = 9.5 Hz, 1H, 4-H pyridazine), 7.60 (d, *J* = 9.5 Hz, 1H, 5-H pyridazine), 7.71-7.77 (m, 4H, 5-(4-chlorophenyl).

3-Chloro-6-[5-(4-nitrophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]pyridazine (11): It was obtained from the reaction of an equimolar quantities (3.46 mmol) of 3-chloro-6-hydrazinylpyridazine (0.5 g) and 3-(4-nitorophenyl)-1-phenylprop-2-en-1-one (**6**) (0.87 g) and piperidine 1.0 mL in 10 mL ethanol. Yield: 0.74 g (57 %); m.p.: 163-168 °C; IR (KBr, ν_{max}, cm^{-1}): 1537, 1355 (-NO_2) 1619, 1490, 3276 2945, 2880 and 1420. MS *m/z* %: 379 [M^+, 100] 381 [M^+, 33].

RESULTS AND DISCUSSION

Pyrazolines (**7-11**) were prepared in good yields by the reaction of respective chalcones (**2-6**) with 3-chloro-6-hydrazinylpyridazine. These were characterized through their spectral data (IR, ^{1}H NMR and mass) while (**7**) in addition gave the expected elemental analysis. The IR spectra displayed the absorption bands for the OH or the NO_2 functionalities. The ^{1}H NMR data was also consistent with the designated structures. The mass spectra of these pyrazolines showed the molecular ion as the base peak together with the M+2 due to ^{37}Cl isotope with the proportionate intensity (3:1).



7-11

(**7**) R_1= R_2= C_6H_5 (**8**) R_1= C_2H_5, R_2= C_6H_5 (**9**) R_1= 4-OHC_6H_4, R_2= C_6H_5 (**10**) R_1= C_6H_5, R_2= 4-ClC_6H_4 (**11**) R_1= C_6H_5, R_2= 4-$NO_2C_6H_4$

Antibacterial activity: These pyrazolines were tested, by disc diffusion method, for their antibacterial properties against various organisms. The results are presented in Table-1.

TABLE-1
ANTIBACTERIAL ACTIVITY OF 1,3,5-TRISUBSTITUTED PYRAZOLINES

Code	Inhibition (%)					
	S. aureus	*E. coli*	*S. typhi*	*P. aureuginosa*	*B. subtilis*	*S. sonnei*
7	45.54	3.12	11.45	15.63	31.80	31.31
8	31.21	14.97	26.31	90.28	52.20	29.45
9	52.64	48.77	54.24	89.26	18.57	46.02
10	47.56	27.07	19.65	90.56	31.13	15.93
11	46.86	14.95	26.28	64.51	12.17	19.49
Ciprofloxacin	96.13	94.14	97.13	91.16	96.48	98.01

Taking ciprofloxacin as the standard only three pyrazolines (**8**), (**9**) and (**10**) were somewhat active and still these were only effective against *P. aureuginosa*. These results seem promising and incentivate preparation of other pyrazolines in this series containing a chloropyridazine substituent in the ring.

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