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ANTIFUNGAL ACTIVITY OF SOME ISOMERIC SPIRO PYRAZOLONES.

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Abstract: 4-Arylmethylene-2,4-dihydro-2 5-disbstituted-3H-pyrazol-3-ones (1a-f : as dipolarophile) react with benzonitrile oxide (2;as 1,3-dipole) to yield E/Z-4.5-dihydrospiro-[3-phenyl-5-substituted phenyl isoxazole-4,4' (2',4'-dihydro-5'-methyl-2'-phenyl/phenyl methyl-3'H-pyrazo-3'-ones)]

Keywords— *Pyrazol, Benzonitrile, Isoxazole, Dipolarophile*

I INTRODUCTION

The importance of pyrazolones chemistry lines in the fact that these have occupied a unique position in heterocyclic chemistry due to their wide applicability in various fields viz. Industry (1), medicinal therapy (2, 3) and agriculture(4). 2,4-Dihydro-3H- pyrazol-3one derivative have physiological properties and have found application as antibacterial(5) antihypertensive (6),antinfammatory(7), anticonvulsant(8) antitumor(9) and antifungal(10) agents. These importances of pyrazolones derivative have promoted us to synthesis title compounds and our attempt in to correlate antibacterial activity and structure of the compounds.1, 3-Dipolar Cycloaddition reactions have been studied to a numerous unsaturated systems leading to five member ring heterocyclic. 1, 3, 4-Arylmethylene-2, 4- dihydro-2, 5-disubstituted -3H-pyrazole-3-ones. [(As dipolarophile) reacted with diphenylnitrilimine (as 1, 3-dipole) to yield two isomers, VIZ E and Z-4, 5-Dihydro spiro-(4-aryl-1, 3-diphenyl pyrazol-5, 4'-(2', 4'-dihydro-2', 5'-disubstituted-3'H-Pyrazole-3'-ones)].

1,3-Dipolar Cycloaddition reaction of 4-arylmethylene-2,4-dihydro-5-methyl-2-phenyl/phenylmethyl-3H-pyrazol-3-ones (1a-f;as dipolarophile) with benzonitrile oxide (2; as 1,3-dipole) resulted in the formation of E/Z 4,5-dihydro spiro [3-phenyl-5-substituted phenyl isoxazole-4,4'-(2',4'-dihydro-5-methyl-2'-phenyl/phenylmethyl-3'H–pyrazole-3'-one] (scheme-1). This reaction is stereo specific as well as stereo selective and the peculiarity of the reaction commanded interest and stimulated to undertake the synthetic process. The benzonitrile oxide (2) is generated in situ by the reaction of benzhydroxamoyl chloride and triethylamine in the presence of dry chloroform at room temperature. The physical and spectral data of the compounds are presented (Table-1).

II EXPERIMENTAL

Melting points were determined on a Buchi apparatus and are uncorrected. Microanalyses were carried out on a Coleman C, H and N-analysers. IR spectra (Nujol) were recorded on Perkin-Elmer-720 and 257 spectrophotometers and PMR spectra (CDCI$_3$) on Varian A-60D and Jeol FX-90Q spectrometers using TMS as an internal standard.

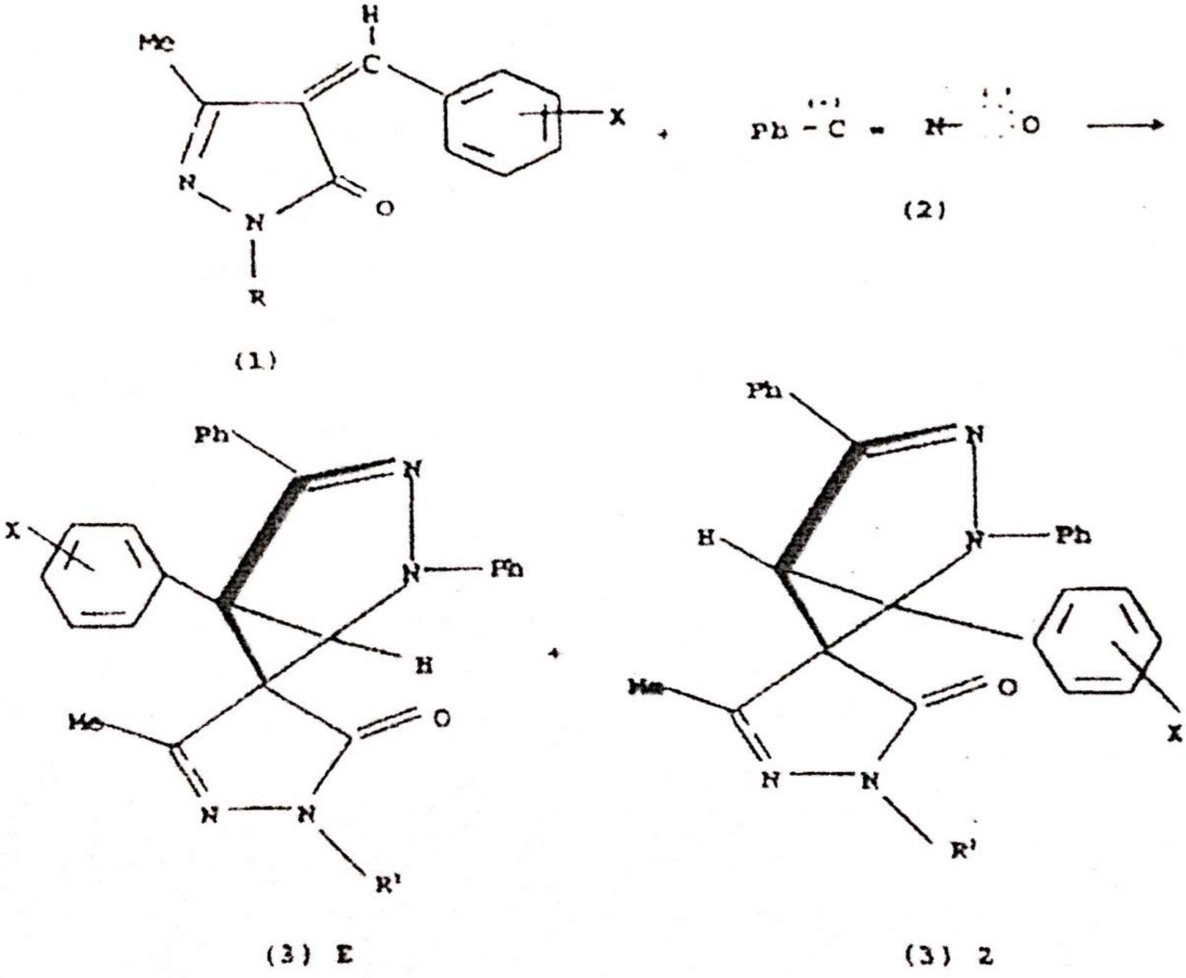
4-Arylmethylene-2, 4-dihydro-2, 5-disubstituted-3H-pyrazol -3-ones (5) (1a-f) and the benzhydroxamoyl chloride (6), were prepared following the standard methods.

E/Z-4,5-dihydro spiro (3-phenyl-5-substituted phenyl isoxazol-4,4'-(2',4'-dihydro-5'-methyl-2'-phenyl/ phenylmethyl-3'H-pyrazol-3'-one)(3a-f).

0.01 Mole (1.01g) of triethylamine was added in one lot into an ice cooled and magnetically will stirred solution of 0.01 mole (1.55g) benzhydroxamoyl chlorides in 50 ml dry ether. The triethylamine hydrochloride started to precipitate immediately. After twenty minutes triethylamine hydrochloride was filtered rapidly and washed with dry ether (2X10ml). 0.01 mole of 4-arylmethylene-2,4-dihydro-2,5-disubstituted-3H-pyrazol-3-ones in 25ml dry chloroform was added immediately in one lot to the filtrate with the exclusion of the moisture. The reaction mixture was stirred for forty eight hours at room temperature. The reacting mixture was filtered to remove any trace of triethylamine hydrochloride. The residue gave two spots on TLC plate, which were different from the starting materials. The product E and Z were separated by column chromatography on silica gel and eluted with benzene; n-hexane (50:50).The product was further purified by TLC and recrystallised from benzene: n-hexane (20:80).

III RESULT AND DISCUSSION

The work already reported by the authors (4,7) reveal that the 1,3-dipolar Cycloaddition of diphenyl nitrile imine with 4-Arylmethylene-2,4-dihydro-5-methyl-2-phenyl/phenylmethyl -3H-pyrazol-3-ones resulted in the formation of two isomers viz E and Z, for E-isomers, the C-5’-methyl proton lies in the shielding zone of C-4, phenyl ring and therefore occurs at high field and low \$-value, while the hydrogen atom at C-4 is deshielded by the anisotropic effect of C-3’-carbonyl group and resonates at low field and high \$-value.



(Scheme-1)

For E-isomers the PMR spectral data (Table-1) show, in general, a singlet(3H) at higher field (lower \$1.34-1.45) for C-5’ methyl protons which falls under shielding zone of phenyl ring at C-5. The fact is supported by the molecular models of E and Z-isomers. Moreover in this configurations the C-5 hydrogen would be deshielded at (\$5.30-5.50) by anisotropic effect of C-3’ carbonyl group as it has been observed in spectrum of the compounds (Table-1), that confirms E-isomer.

The PMR spectral data (Table-1) show in general for Z-isomer a singlet (3H) at (2.06-2.08)for C-5’ methyl protons a singlet (1H) at (4.62-4.74)for phenyl methylene proton at C-5, and multiplet at $(6.66-8.00) for aromatic protons. Since C-5’ methyl protons and C-5 hydrogen resonate at normal $ (2.06-2.08) and $(4.62-4.74) ppm, respectively. The C-5’-methyl protons are not shielded by C-5-phenyl ring supporting Z- Configuration for the product at N-2 magnetically non equivalent. The appearance of an AB quarted J_{AB} = (12-14 H_Z) whereas in Z-isomers. These two phenyl methyl protons at N-2’ would be in symmetrical environment that resonates a singlet at $ (4.46-4.50) which is proved by molecular model of the compound.

Compounds	R^1	X
3(a)	Ph	H
3(b)	Ph	p-OMe
3(c)	Ph	p-NO_2
3(d)	Ph	p-$N<^{Me}_{Me}$
3(e)	CH_2Ph	p-$OMe<_{Me}^{Me}$
3(f)	CH_2Ph	p-$N<^{Me}_{Me}$

TABLE – 1

Comp No.	Yield (%)	Isomer	M.P.(^OC)	I.R.(Nujol) U_{max}, Cm^{-1}	UV(MeOH) nm ƛm ax^1	PMR($CDCI_3$)& (ppm)
3a	60	E	148	1725(>C=O), (>C=N)1600s, 1300m,1140m, 1060w & 740w	247, 300 & 326	1.45(S,3H,CH_3); 5.45(S,1H,CH); 8.20(m,20H,20ArH)
		Z	166-167	1720(>C=O), 1600(>C=N) 1300m,1140m, 1060w & 740w	243, 300 & 325	2.21 (S,3H,CH); 5.10(S,1H,CH); 9.78(m,20H,20ArH)
3b	65	E	185	1715(>C=O), 1600(>C=N), 1600s, 1490s, 1300w, 1280s 1180w, 1120w, 1030w, 830s & 740m	240, 298 & 326	1.50(S,3H,CH_3); 3.80(S,3H,OCH_3); 5.10(S,1H,CH); 6.80-8.20(m,19H,19ArH)
		Z	167	1725(>C=O), 1600(>C=N), 1500s, 1310w, 1210m, 1180w, 1140w, 1040w, & 740m	242, 298 & 326	2.30(S,3H,CH_3); 3.70(S,3H,OCH_3); 5.10(S,1H,CH); 6.80-8.20(m,19H,19ArH)
3c	64	E	137	1720(>C=O), 1600(>C=N), 1500s, 1345s, 1140w, 1260w & 850m	240 & 236	1.50(S,3H,CH_3); 5.50(S,1H,CH); 7.00-8.20(m,19H,19ArH)
		Z	178-180	1715(>C=O), 1595(>C=N), 1500s, 1345w, 1140w, 1260w & 850w	240 & 236	2.20(S,3H,CH_3); 5.10 (S,1H,CH); 7.00-8.20(m,19H,19ArH)
3d	69	E	179-180	1725(>C=O), 1600(>C=N), 1500s, 1300w, 1140w, 1060w & 740m	247, 300 & 330	1.48(S,3H,CH_3); 2.90(S,1H,$N<^{Me}_{Me}$); 5.36(S,1H,CH); 6.50-7.97(m,19H,19ArH)
		Z	148	1720(>C=O), 1600(>C=N), 1520s ,1500s, 1290s, 1230m, 1190m, 1120m, 1050w 1000w, 910w & 810m	247, 300 & 330	2.15(S,3H,CH_3); 2.80(S,6H,$N<_{Me}^{Me}$) 6.80-8.20(m,19H,19ArH)

3e	62	E	185-186	1730(>C=O), 1610(>C=N), 1515s, 1320m, 1280m, 1200w, 1140w, 1080w, 1045w, 850w & 720m	232, 285 & 330	1.34(S,3H,CH_3); 3.78(S,3H,OCH_3); Centered at 4.92(AB quartet 2H, CH_2 J_{AB}=12Hz)) 5.30(S,1H,CH);& 6.70-7.60
		Z	163-165	1725(>C=O), 1610(>C=N) 1510s,1300w, 1270s, 1200m, 1085w, 1000w, 850w & 710m	232, 285 & 330	2.80(S,3H,CH_3); 3.80(S,3H,OCH_3); 4.60(S,2H,CH_2); 5.00(S,1H,CH);& 6.70-7.60(m,19H,19ArH)
3f	**65**	**E**	179-180	1710(>C=O), 1600(>C=N) 1107m, 1040m & 740m	232, 270 & 330	1.37(S,3H,CH_3); 2.93(S,6H,$N<^{Me}_{Me}$); Centered at 4.93(AB quartet 2H, CH_2 J_{AB}=14Hz)) 5.33(S,1H,CH); 7.55(m,19H,19ArH)
		Z	184	1720(>C=O),1600(>C=N) 1500s, 1300m, 1720w, 1170w, 1120w, 1060m & 810m	232, 270 & 330	2.04(S,3H,CH_3); 2.90(S,6H,$N<^{Me}_{Me}$); 4.42(S,2H,CH_2); 4.93(S,1H,CH);& 6.44-7.55(m,19H,19ArH)
All compounds gave satisfactory C, H & N analysis.						

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