



SYNTHESIS AND CHARACTERIZATION 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-PYRAZOL-3'-ONES)]

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ABSTRACT

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

1, 3-Dipolar cycloaddition reactions have been studied in numerous unsaturated systems leading to five-membered ring heterocycles. 1-3,4-Arylmethylene-2,4-dihydro-2,5-disubstituted-3H-pyrazol-3-one (as dipolarophile) reacted with diphenyl nitrile imine (as 1,3-dipole) to yield two isomers VIZ. E and Z-4,5-dihydro spiro-[4-aryl-1,3-diphenyl pyrazole-5,4'-(2',4'-dihydro-2',5'-disubstituted -3'H-pyrazol-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)] (3)(scheme-1).^{I-VIII}

This reaction is stereospecific as well as stereoselective and the peculiarity of the reaction commanded interest & 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 the room temperature. The physical and spectral data of the compounds are presented (Table 1).^{IX-XXII}

EXPERIMENTAL

Melting points were determined on a Buchi apparatus and were uncorrected. Microanalyses were carried out on Coleman C, H, and N-analysers. IR spectra (Nujol) were recorded on Perkin-Elmer-720 and 257 spectrophotometers and PMR spectra (CDCl₃) 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-ones⁵ (1a-f), and the benzhydroxamoyl chloride⁶, 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'-penyl/phenylmethyl-3'H-pyrazol-3'-one)](3a-f). 0.01 mol (1.01g) of

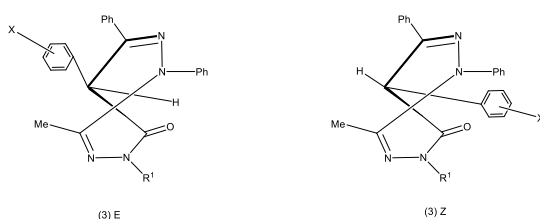
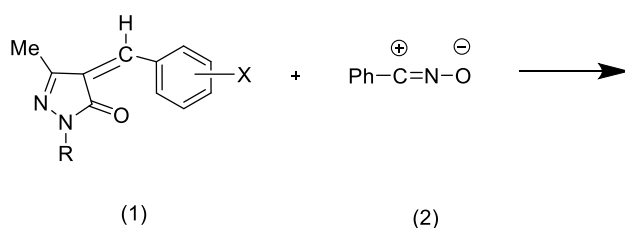
triethylamine was added in one lot into an ice-cooled and magnetically well-stirred solution of 0.01 mol (1.55g) benzhydroxamoyl chloride in 50 ml dry ether. The triethylamine hydrochloride started to precipitate immediately. After twenty minutes triethylamine hydrochloride was filtered rapidly and washed with dry ether (2x10ml). 0.01 mol of 4-arylmethylene-2,4-dihydro-2,5-disubstituted-3H-pyrazol-3-ones in 25 ml 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 reaction mixture was filtered to remove any trace of triethylamine hydrochloride. The residue gives two spots on the TLC plate, which were different from the starting materials. The products 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 recrystallized from benzene; n-hexane (20:80).

RESULT & 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 δ -values, 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 δ -value.

For E-isomers the PMR spectral data (Table-1) show, in general, a singlet(3H) at higher field (lower δ 1.34-1.45) for C-5'-methyl protons which fall under the shielding zone of the phenyl ring at C-5. The fact is supported by the molecular models of E & Z-isomers. Moreover, in this configuration, the C-5 hydrogen would be deshielded at (δ 5.30-5.50) by the anisotropic effect of C-3' carbonyl group as it has been observed in the spectrum of the compound (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, singlet(1H) at (4.62-4.74) for phenyl methylene proton at C-5, and multiplet at (δ 6.66-8.00) for aromatic protons. Since C-5'-methyl protons and C-5-hydrogen resonate at normal δ (2.06-2.08) and δ (4.62-4.74) ppm respectively. The C-5'-methyl protons are not shielded by the C-5-phenyl ring, supported Z-configuration for the product at N-2 magnetically non-equivalent. The appearance of AB quartet $J_{AB}=(12-14 \text{ Hz})$ whereas in Z-isomers. These two phenyl methyl protons at N-2' would be in a symmetrical environment that resonates a singlet at (δ 4.46-4.50) which is proved by the molecular model of the compound.



Compounds	R ¹	X
3(a)	Ph	H
3(b)	Ph	<i>P</i> -OMe
3(c)	Ph	<i>P</i> -NO ₂
3(d)	Ph	<i>P</i> -NMe ₂
3(e)	CH ₂ Ph	<i>P</i> -OMe

Compound No.	Yield (%)	Isomer	M.P (°C)	I.R. (Nujol) ν_{\max} , Cm^{-1}	UV (MeOH) nm λ_{\max}^{-1}	PMR (CDCl_3), $\delta(\text{ppm})$
3(a)	60	E	148	1725(>c=O),(>c=N) 1600s, 1300m, 1140m, 1060w and 740m	247, 300 & 326	1.45(S,3H,CH ₃), 5.45(s,1H,CH) 6.90-8.20 (m,20H,20ArH)
		Z	166-167	1720(>C=O) 1600(>C=N) 1300m 1140w, 1060w and 740 w	243, 300 & 325	2.21(S,3H,CH ₃), 5.10(S, 1H, CH) 6.88-9.78 (m, 20H, 20ArH)
3(b)	65	E	185	1715 (>C=O) 1600(>C=N) 1600s, 1490s, 1300w 1280s, 1180w, 1120w, 1030w, 830s and 740 m	240, 298 & 326	1.50 (S, 3H, CH ₃), 3.80 (S, 3H, OCH ₃) 5.40(S, 1H, CH), 6.80-8.20 (m ,19H, 19ArH)
		Z	167	1725 (>C=O) 1600(>C=N) 1500s, 1310w 1210m, 1180w, 1140w, 1040w, and 740 m	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)
3(c)	64	E	137	1720(>C=O), 1600(>C=N), 1500s, 1345s, 1140w, 1260 and 850w	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 240, 236 1345s, 1140w and 850w	240 & 236	2.20(S,3H,CH ₃) 5.10(S, 1H,CH) 7.00-8.20 (m, 19H 19ArH)
3(d)	69	E	179-180	1725(>C=O) 1600(>C=N) 1500s 1300w, 1140w, 1060w and 740m	247, 300 & 330	1.49(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 and 810m	247, 300 & 330	2.15 (S,3H, CH ₃) 2.80 (S, 6H,N< ^{Me} _{Me}) 5.10(S, 1H, CH) 6.80-8.20 (m,19H),19ArH)
3(e)	62	E	185-186	1730(>C=O) 1610(>C=N) 1515s 1320m, 1280m, 1200w, 1140w, 1080w 1045w, 850w and 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)

						and 6.70-7.60 (m,19H,19ArH)
		Z	163-165	1725(>C=O) 1610(>C=O), 1510s 1300w, 1270s, 1200m,1085w,1000 w 850w and 710m	232, 285 & 330	2.08(S,3H,CH ₃) 3.80(S,3H,OCH ₃) 4.60(S,2H,CH ₂) 5.00(S,1H,CH) and 6.76- 7.60(m,19H,19Ar H)
3(f)	65	E	179-180	1710(>C=O) 1600(>C=N) 1107m, 1040m and 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) and 6.53-7.79 (m,19H,19ArH)
		Z	184	1720(>C=O), 1600(>C=N), 1500s 1300m, 1270w, 1170w 1120w, 1060m and 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) and 6.44- 7.55(m,19H,19Ar H)
All compounds gave satisfactory C, H & N analyses.						

Table 2 Physical & Spectral Data of Compounds (3a-f)**CONCLUSION:**

In summary we have developed a regioselective 1,3-dipolar cycloaddition reaction of 1-3,4-Arylmethylene-2,4-dihydro-2,5-disubstituted-3H-pyrazol-3-one (as dipolarophile) reacted with diphenyl nitrile imine

AKS and VPS acknowledge the Department of Chemistry, Faculty of Engineering & Technology, VBS Purvanchal University, Jaunpur (U.P) for providing the necessary facility to conduct this research.

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Received on December 10, 2022.