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1,3-Dipolar Cycloaddition Reaction of Benzonitrile Oxide with 4-Arylmethylene-2,4-dihydro-2,5-disubstituted-3*H*-pyrazol-3-ones

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In this paper, enantioselective formation of E/Z-4,5-dihydro spiro[3- phenyl-5-substituted phenyl isoxazole-4,4'-(2',4'-dihydro-2',5'-disubstituted-3'*H*-pyrazol-3'-ones)] is described by means of stereospecific 1,3-dipolar cycloaddition of benzonitrile oxide with 4-arylmethylene-2,4-dihydro-2,5-disubstituted-3*H*-pyrazol -3-ones.

Key Words: Substituted pyrazolones, Cycloaddition, Configurational isomers, Stereospecific.

INTRODUCTION

1,3-Dipolar cycloaddition reactions with a unsaturated system leading to five membered ring heterocycles have been widely studied[1-3]. The 1,3-dipolar cycloaddition reaction of diphenyl nitrileimine has been reported in which 4-arylmethylene-2,4-dihydro-2,5-disubstituted-3*H*-pyrazol-3-ones (as dipolarophile) react with diphenyl nitrileimine (as 1,3-dipole) to yield two stereoisomers[1,4,5] *viz.*, E and Z-4,5-dihydrospiro [4-aryl-1,3-diphenyl pyrazole-5,4'-(2',4'-dihydro-2',5'-disubstituted-3'*H*-pyrazol-3'-ones)]. Herein, an attempt is made to synthesize the two configurational isomers, *viz.*, E and Z-4,5-dihydro spiro[3-phenyl-5-substituted phenyl isoxazole-4,4'-(2',4'-dihydro -2',5'-disubstituted-3'*H*-pyrazol-3'-ones)](**3a-l**) and (**4a-l**), respectively, by the 1,3-dipolar cycloaddition reaction of benzonitrile oxide (**2**) (as 1,3-dipole) with 4-arylmethylene-2,4-dihydro-2,5-disubstituted-3*H*-pyrazol-3-ones (**1a-l**) (as dipolarophile). This reaction is stereospecific as well as stereoselective. The peculiarity of the reaction commanded interest and stimulated to undertake the synthetic process.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Micro analyses were carried out on Coleman C, H and N analyzers. IR

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spectra (Nujol) were recorded on Perkin-Elmer 720 and 257 spectrophotometers and PMR spectra ($CDCl_3$) were recorded on a Varian A-60D and Jeol FX-90Q spectrometers using TMS as an internal standard. 4-Aryl mthylene-2,4-dihydro-2,5-disubstituted-3*H*-pyrazol -3-ones[6,7] (**1a-d**) and benzhydroxamoyl chloride[8] were prepared following the standard methods.

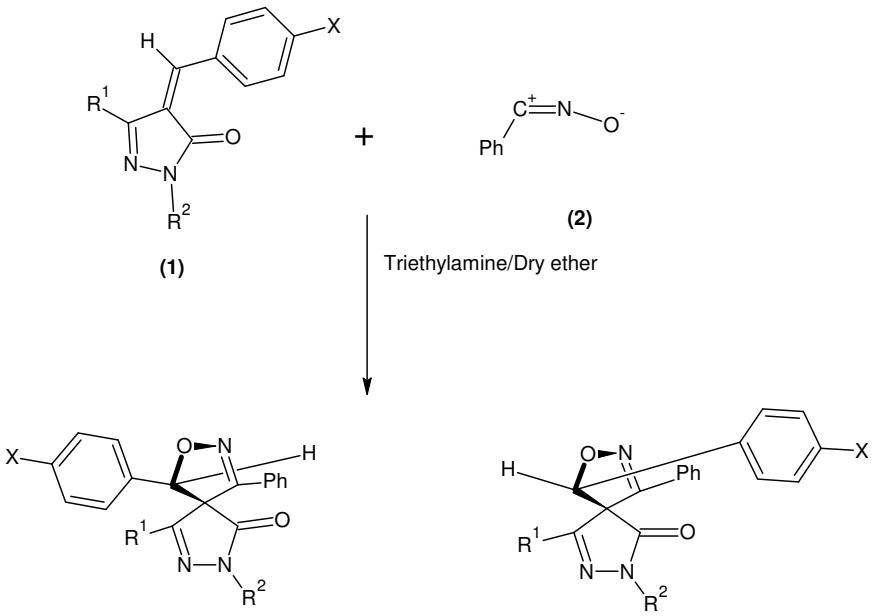
E/Z-4,5- Dihydro spiro [3-phenyl-5-substituted phenyl isoxazole-4,4'-(2',4'-dihydro-2',5'-disubstituted-3'*H*-pyrazol-3'-ones)] (**3a-l**) and (**4a-l**) were prepared by known method[5].

0.05 mol (0.05 g) of triethylamine was added into an ice cooled and magnetically well stirred solution of 0.05 mol (7.75 g) benzhydroxamoyl chloride in 100 mL dry ether. The triethylamine hydrochloride started to precipitate immediately. After 20 min, triethylamine hydrochloride was filtered and washed with dry ether (2 × 10 mL). 0.05 mol of 4-arylmethylene-2,4-dihydro-3*H*-pyrazol-3-ones in 50 mL dry chloroform was added to the filtrate with the exclusion of the moisture. The reaction mixture was stirred for 48-50 h at room temperature and filtered to remove any trace of triethylamine hydrochloride. The solvent was evaporated under reduced pressure on rotary evaporator. The residue gave two spots on TLC plate. One spot was corresponding to E-isomer and the other to Z-isomer of 4,5-dihydro-spiro[-3-phenyl-5-substituted isoxazol-4,4'-(2',4'-dihydro-2',5'-disubstituted-3'*H*-pyrazol-3'-ones)]. The E and Z isomers were separated by column chromatography on silica gel and eluted with benzene:*n*-hexane (50:50) mixture. The products were further purified by TLC and recrystallized from benzene:*n*-hexane (20:80). The analytical and spectral data are recorded in Table-1.

RESULTS AND DISCUSSION

The work already reported by the authors[1,5] reveal that the 1,3-dipolar cycloaddition of diphenyl nitrile-imine with 4-arylmethylene-2,4-dihydro-2,5-disubstituted-3*H*-pyrazol-3-ones resulted in the formation of two stereoisomers, *viz.*, E and Z-spiro pyrazole-pyrazolones. For E-isomer, the C-5'-methyl protons lies in the shielding zone of C-4 phenyl ring and therefore occurs at high field and low δ-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 δ-value[5].

1,3-Dipolar cycloaddition reaction of benzonitrile oxide (**2**) with 4-aryl mthylene-2,4-dihydro-2,5-disubstituted-3*H*-pyrazol-3-ones (**1a-l**) in the presence of dry ether was carried out, which resulted in the formation of two stereoisomers, namely, E and Z-4,5-dihydro spiro[3-phenyl-5-substituted phenyl isoxazole-4,4'-(2',4'-dihydro-2',5'-disubstituted-3'-pyrazol-3'-ones)] (**3a-l**) and (**4a-l**), respectively (**Scheme-I**).



Compd. No.	R_1	R_2	X
a	CH_3	Ph	H
b	CH_3	Ph	*p*-NO_2
c	CH_3	Ph	*p*-OMe
d	CH_3	Ph	*p*-$N(Me)_2$
e	CH_3	Ch_2Ph	H
f	CH_3	Ch_2Ph	*p*-NO_2
g	CH_3	Ch_2Ph	*p*-OMe
h	CH_3	Ch_2Ph	*p*-$N(Me)_2$
i	Ph	Ph	H
j	Ph	Ph	*p*-NO_2
k	Ph	Ph	*p*-OMe
l	Ph	Ph	*p*-$N(Me)_2$

Scheme-I

For E-isomer, the PMR spectral data (Table-1) show, in general, a singlet (3H) at higher field (lower δ, 1.34-1.50 ppm) for C-5' methyl protons which falls under shielding zone of phenyl ring at C-5. Moreover, in this configuration, the C-5-hydrogen would be deshielded at δ 5.30-5.50 ppm by anisotropic effect of C-3' carbonyl group as it has been observed in the spectrum of the compounds that confirms the formation of E-isomers.

For Z-isomer, the PMR spectral data (Table-1) show a singlet (3H) at δ 2.06-2.08 ppm for C-5'-methyl protons, a singlet H at δ 4.62-4.74 ppm for phenyl methylene proton at C-5 and multiplet at δ 6.60-8.00 ppm for aromatic

TABLE-1
E AND Z-4, 5-DIHYDRO SPIRO[3-PHENYL-5-SUBSTITUTED PHENYL ISOXAZOLE-4, 4'-(2', 4'-DIHYDRO-2', 5'-DISUBSTITUTED-3'*H*-PYRAZOL-3'-ONES)]

R_1	R_2	X	Isomer	m.p. (ºC)	Yield (%)	IR (Nujol, ν_{max}, cm^{-1})	PMR ($CDCl_3$), δ (ppm)
CH_3	C_6H_5	H	E	148	60	1725 (s, >C=O), 1600 (s, >C=N)	1.45 (s, 3H, CH_3), 5.45 (s, 1H, CH), 6.90-8.20 (m, 15H, 15ArH).
			Z	174	35	1720 (s, >C=O), 1600 (s, >C=N)	2.21 (s, 3H, CH_3), 5.10 (s, 1H, CH), 6.88-9.78 (m, 15H, 15ArH).
CH_3	C_6H_5	*p*-NO_2	E	137	64	1720 (s, >C=O), 1600 (s, >C=N)	1.50 (s, 3H, CH_3), 5.50 (s, 1H, CH), 7.00-8.20 (m, 14H, 14ArH).
			Z	166	30	1715 (s, >C=O), 1595 (s, >C=N)	2.20 (s, 3H, CH_3), 5.10 (s, 1H, CH), 7.00-8.00 (m, 14H, 14ArH).
CH_3	C_6H_5	*p*-OMe	E	185	65	1715 (s, >C=O), 1600 (s, >C=N)	1.50 (s, 1H, CH_3), 3.80 (s, 3H, OCH_3); 5.40 (s, 1H, CH), 6.80-8.26 (m, 14H, 14ArH).
			Z	175	30	1725 (s, >C=O), 1600 (s, >C=N)	2.30 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3); 5.10 (s, 1H, CH), 6.80-8.20 (m, 14H, 14ArH).
CH_3	C_6H_5	*p*-$N(CH_3)_2$	E	180	62	1725 (s, >C=O), 1600 (s, >C=N)	1.49 (s, 3H, CH_3), 2.90 (s, 6H, -$N(CH_3)_2$; 5.36 (s, 1H, CH), 6.50-7.95 (m, 14H, 14ArH).
			Z	148	30	1720 (s, >C=O), 1600(s, >C=N)	2.15 (s, 3H, CH_3), 2.80 (s, 6H, -$N(CH_3)_2$; 5.10 (s, 1H, CH), 6.80-8.70 (m, 14H, 14ArH).
CH_3	$-CH_2C_6H_5$	H	E	150	61	1730 (s, >C=O), 1600 (s, >C=N)	1.46 (s, 3H, CH_3), Centered at 4.95 (AB quartet, 2H, CH_2, J_{AB} = 12Hz); 5.37 (s, 1H, CH), 6.75-7.68 (m, 15H, 15ArH).
			Z	176	35	1725 (s, >C=O), 1600 (s, >C=N)	2.07 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 5.20 (s, 1H, CH), 6.82-7.90 (m, 15H, 15ArH).

CH_3	$-CH_2C_6H_5$	*p*-NO_2	E	142	60	1725 (s, >C=O), 1605 (s, >C=N)	1.38 (s, 3H, CH_3), Centered at 4.94 (AB quartet, 2H, CH_2, J_{AB} = 14Hz); 5.34 (s, 1H, CH), 6.65-7.80 (m, 14H, 14ArH).
			Z	160	35	1720 (s, >C=O), 1605 (s, >C=N) .	2.10 (s, 3H, CH_3), 4.58 (s, 2H, CH_2), 5.10 (s, 1H, CH), 6.82-7.95 (m, 14H, 14ArH).
CH_3	$-CH_2C_6H_5$	*p*-OMe	E	185	60	1730 (s, >C=O), 1610 (s, >C=N)	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 (m, 14H, 14ArH).
			Z	164	35	1725 (s, >C=O), 1610 (s, >C=N)	2.08 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.60 (s, 2H, CH_2), 5.00 (s, 1H, CH), 6.76-7.60 (m, 14H, ArH).
CH_3	$-CH_2C_6H_5$	*p*-$N(CH_3)_2$	E	180	62	1715 (s, >C=O), 1600 (s, >C=N)	1.37 (s, 3H, CH_3), 2.90 (s, 6H, -$N(CH_3)_2$); Centered at 4.93 (AB quartet, 2H, CH_2, J_{AB}=14Hz); 5.33 (s, 1H, CH) & 6.53 - 7.79 (m, 14H, 14ArH).
			Z	184	32	1710 (s, >C=O), 1600 (s, >C=N)	2.04 (s, 3H, CH_3), 2.96 (s, 6H, -$N(CH_3)_2$); 4.42 (s, 2H, CH_2), 5.00(s, 1H, CH), 6.44-7.55 (m, 14H, 14ArH).
Ph	Ph	H	E	160	60	1730 (s, >C=O), 1600 (s, >C=N),	5.40 (s, 1H, CH), 6.60-8.30 (m, 20H, 20ArH).
			Z	183	36	1725 (s, >C=O), 1600 (s, >C=N),	5.00 (s, 1H, CH), 6.60-8.30 (m, 20H, 20ArH).
Ph	Ph	*p*-NO_2	E	146	65	1725 (s, >C=O), 1600 (s, >C=N),	5.38 (s, 1H, CH), 6.72-8.40 (m, 19H, 19ArH).
			Z	173	30	1720 (s, >C=O), 1600 (s, >C=N),	5.00 (s, 1H, CH), 6.60-8.30 (m, 19H, 19ArH).
Ph	Ph	*p*-OMe	E	184	64	1730 (s, >C=O), 1600 (s, >C=N),	3.78 (s, 3H, OCH_3), 5.40 (s, 1H, CH), 6.80-8.40 (m, 19H, 19ArH).
			Z	176	30	1725 (s, >C=O), 1600 (s, >C=N),	3.80 (s, 3H, OCH_3), 5.10 (s, 1H, CH), 6.70-8.30 (m, 19H, 19ArH).
Ph	Ph	*p*-$N(CH_3)_2$	E	180	65	1725 (s, >C=O), 1600 (s, >C=N),	2.90 (s, 6H, -$N(CH_3)_2$), 5.42 (s, 1H, CH), 6.74-8.40 (m, 19H, 19ArH).
			Z	193	32	1720 (s, >C=O), 1600 (s, >C=N), .	2.92 (s, 6H, -$N(CH_3)_2$), 5.30 (s, 1H, CH), 6.70-8.37 (m, 19H, 19ArH).

The analytical values for C, H and N gave satisfactory results in the E and Z isomers.

protons. Since C-5'-methyl protons and C-5-hydrogen resonates at normal δ 2.06-2.08 ppm and δ 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. This fact is supported by the molecular model of E and Z-isomers.

It is noteworthy that the phenyl methyl protons at N-2' become magnetically non-equivalent in compounds **3e-h** and it appears as a AB quartet J_{AB} = (12-14 Hz) in E-isomers, whereas in Z-isomers these two phenyl methyl protons at N-2' would be in symmetrical environment that resonates a singlet at δ 4.46-4.50 ppm, which is proved by molecular model of the compounds.

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REFERENCES

1. P.L. Anelli and P.D. Croce, *Gazz. Chim. Ital.*, **111**, 269 (1981).
2. K.N. Houk, J. Sims, C.R. Watts and L.J. Luskus, *J. Am. Chem. Soc.*, **95**, 7301 (1973).
3. R. Huisgen, *Angew, Chem. Int. Ed. Engl.*, **2**, 565 (1963).
4. R. Huisgen, R. Grashey and J. Saver, in ed.: S. Patali, In The Chemistry of Alkenes, Interscience, New York (1964).
5. D. Singh and D. Singh, *J. Indian Chem. Soc.*, **68**, 580 (1991).
6. D. Singh and D. Singh, *J. Chem. Eng. Data*, **29**, 355 (1984).
7. D. Singh and D. Singh, *J. Indian Chem. Soc.*, **68**, 165 (1991).
8. H. Rheinboldt, M. Dewald, F. Jansen and O. Schmitz-Dumont, *Ann. Der. Chem.*, **451**, 161 (1927).

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