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Microwave Accelerated 1,3-Dipolar Cycloaddition Reactions of Cyclopentylidene N-Phenyl Nitrone with Substituted N-Arylmaleimides

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Microwave accelerated 1,3-dipolar cycloaddition reactions of cyclopentylidene N-phenyl nitrone with substituted N-arylmaleimides leading to synthesis of new 2,5-diaryl-3, 3-spirotetramethylene-4H-2,3,3a, 5,6,6a-hexahydropyrrolo[3,4-d] isoxazole-4, 6-dione derivatives.

Key Words: Maleimides, Microwave accelerated, Nitrones, 1,3-Dipolar cycloadition.

INTRODUCTION

1,3-Dipolar cycloaddition reactions of cyclopentylidene N-phenyl nitrones (**1**) with substituted N-arylmaleimides (**2**) provide new regioisomeric 2,5-diaryl-3,3-spirotetramethylene-4H-2,3,3a,5,6,6a-hexahydropyrolo[3,4-d] isoxazole-4,6-dione derivatives both under conventional and microwave accelerated conditions. Under microwave irradiation reaction completes within 90-150 s with improved yield. While the reaction needs prolonged heating with lower yield under conventional heating. These regioisomers have been characterized on the basis of their spectral measurements.

1,3-Dipolar cycloaddition reactions have been of immense value in the synthesis of heterocyclics[1,2]. This Huisgen reaction of nitrones with varieties of dipolarophiles yields isoxazolidine and isoxazoline derivatives[3-7], generating new steriogenic centers in the products[8]. A survey of literature showed that 1,3-dipolar cycloaddition reactions of cyclopentylidene N-phenyl nitrones with various substituted N-arylmaleimides have not been reported so far. For this reaction various substituted maleimides have been synthesized as reported in literature[9], where as respective nitrones have been obtained by condensing cyclopentanone with various substituted N-phenylhydroxylamines[10].

1,3-Dipolar cycloaddition reactions of these nitrones (**1**) with corresponding N-arylmaleimides (**2**) have been carried out under microwave irradiated and by refluxing equivocal amounts of the dipoles and dipolarophiles in dry toluene. Time required under microwave conditions ranges from 90-150 s as compared to the conventional mode of heating which needs 12 or more hours to mark the completion of reaction. Usual work up of the reaction mixture provides the crude product (**3a-o**) witch on recrystallization from petroleum ether provides only regioisomers (**3a-o**). These products (**3a-o**) have been characterized through their melting points, elemental analyses, IR and ^{1}H NMR spectra. These regioisomers have identical IR spectra and display similar patron for ^{1}H NMR spectra with sharp different melting points and elemental analyses in each case (Table-1). In their IR absorption spectra these 2,5-diaryl-3, 5-spirotetramethylene 4H-2, 3,3a, 5,6,6a-hexahydropyrrolo[3,4-d] isoxazole-4,6-diones show strong absorption bands in the region 1710-1700 cm^{-1}, which have been assigned to the two carbonyl functions which present the imides moiety of these cycloadducts. IR absorption bands in the region 1610-1598 cm^{-1} are due to the skeletal vibrations of the aromatic rings and absorption bands in the region 1540-1530 and 1360-1340 cm^{-1} have been assigned to asymmetric vibrations of the nitro group. Absorption bands in the region 1295-1230 and 1220-1140 cm^{-1} have been assigned to aromatic and aliphatic ether stretching vibrations, respectively.

In the $^{-1}$H NMR spectrum of 2-phenyl-5-anisyl-3,5-spirotetramethylene-4H-2,3,3a, 5,6,6a-hexahydropyrrolo[3,4-d] isoxazole-4, 6-dione displays a multiplet at δ 7.25-6.9 (equivalent to 9H, Ar-H), a doublet at δ 5.6-4.93 (equivalent to 1H, H6a) due to coupling with H_{3a} (JH6a-H_{3a} *ca.* 7.62 cps), another doublet at δ 3.5-3.4 (equivalent to 1H, H_{3a}) due to coupling with H_{6a} (JH3a H_{6a} ~ 7.03 cps), a singlet at δ 3.82 (equivalent to 3H, -OCH_3) and a broad multiplet at δ 2.0-1.2 (equivalent to 8H due to tetramethylene skeleton in cyclopentane moiety)

In all these products proton, H_{6a} shows a high field ranging from 0.7-1.2 ppm as compared to chemical shift of H_{3a} proton, which may be attributed to the fact that carbon which is covalently bonded to oxygen on one side and to carbonyl function on other side, so H_{6a} is deshielded to grater extent as compared to H_{3a}.

EXPERIMENTAL

The infrared spectra of the synthesized compounds have been recorded on FT-IR Perkin-Elmer spectrophotometer RX-I at Department of Chemistry, Punjabi University, Patiala. The proton magnetic resonance spectra have been run on a Bruker AC-400 NMR spectrometer 400 MHz using TMS as an internal standard and $CDCl_3$ + DMSO as a solvent by SAIF, Punjab University, Chandigarh. Mass spectra were recorded on mass spectrometer VG-70S by NIPER, Mohali. The elemental analyses have been carried out at the Microanalytical Laboratory by SAIF, Punjab University Chandigarh. All melting points have been recorded by Gallen-Kamp apparatus and are uncorrected.

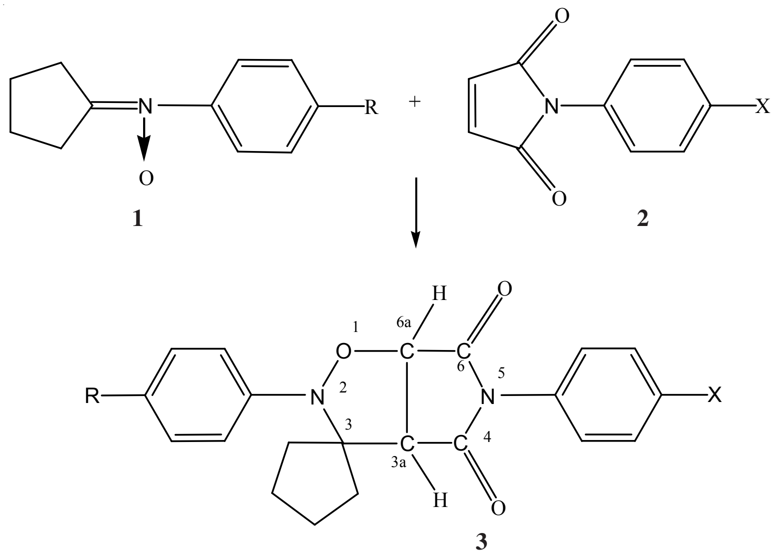
TABLE-1
PHYSICAL AND ANALYTICAL DATA OF 2,5-DIARYL-3,3-SPIROTETRAMETHYLENE-4H, 2,3,3A, 5,6,6a-HEXAHYDROPYRROLO[3,4-D] ISOXAZOL-4, 6-DIONE DERIVATIVES

Compd.	X	R	Microwave		Conventional		m.p. (ºC)	m.f.	Anal. (%) Calcd. (Found)		
			Time (s)	Yield (%)	Time (h)	Yield (%)			C	H	N
3a	H	H	90	80	10	60	175-177	$C_{21}H_{20}N_2O_3$	72.41 (72.33)	5.75 (5.71)	8.04 (8.01)
3b	NO_2	H	120	84	11	72	195-196	$C_{21}H_{19}N_3O_5$	64.12 (64.07)	4.83 (4.81)	10.69 (10.62)
3c	CH_3	H	120	72	11	58	218-220	$C_{22}H_{22}N_2O_3$	72.93 (72.33)	6.08 (6.03)	7.73 (7.71)
3d	Cl	H	90	82	10	62	190-192	$C_{21}H_{19}N_2O_3Cl$	65.88 (65.84)	4.97 (4.90)	7.32 (7.27)
3e	OCH_3	H	90	86	10	78	151-152	$C_{22}H_{22}N_2O_9$	69.84 (69.77)	5.83 (5.84)	7.40 (7.35)
3f	H	CH_3	150	78	12	55	155-156	$C_{22}H_{22}N_2O_3$	72.93 (72.86)	6.08 (6.01)	7.73 (7.70)
3g	NO_2	CH_3	150	81	12	65	145-146	$C_{22}H_{21}N_3O_5$	64.86 (64.72)	5.16 (5.15)	10.32 (10.31)
3h	CH_3	CH_3	150	86	12	64	148-150	$C_{23}H_{24}N_2O_3$	73.40 (73.29)	6.38 (6.37)	7.45 (7.42)
3i	Cl	CH_3	150	82	12	62	133-134	$C_{22}H_{21}N_2O_3Cl$	66.58 (66.43)	5.30 (5.27)	7.06 (7.07)
3j	OCH_3	CH_3	150	90	12	52	138-140	$C_{23}H_{24}N_2O_9$	70.41 (70.39)	6.12 (6.10)	7.15 (7.13)
3k	H	Cl	100	91	11	70	155-156	$C_{21}H_{19}N_2O_3Cl$	65.88 (85.77)	4.97 (4.92)	7.32 (7.27)
3l	NO_2	Cl	150	76	12	56	148-151	$C_{21}H_{18}N_3O_5Cl$	58.95 (58.85)	4.21 (4.18)	9.82 (9.82)
3m	CH_3	Cl	100	85	11	60	135-140	$C_{22}H_{21}N_2O_3Cl$	66.58 (65.54)	5.30 (5.31)	7.06 (7.01)
3n	Cl	Cl	100	90	11	72	210-212	$C_{21}H_{18}N_2O_3Cl$	60.43 (60.28)	4.32 (4.29)	6.71 (6.65)
3o	OCH_3	Cl	90	87	11	64	138-140	$C_{27}H_{21}N_2O_4Cl$	64.00 (63.01)	5.10 (5.02)	6.79 (6.73)

General procedure for the synthesis of 2-phenyl-5-(4-chlorophenyl)-3,3-spirotetramethylene-4H-2,3,3a,5,6,6a-tetrahydropyrrolo[3,4-d]isoxazol-4,6-dione: This Huisgen reaction was carried out under both conventional and microwave accelerated conditions following a similar procedure in each case. A typical procedure is described under both conditions.

Scheme-I: Tetramethylene-N-phenyl nitron (0.01 mol) contained in 100 mL conical flask were added N-4-chlorophenylmaleimide (0.01 mol) and sodium dried toluene (50 mL). The reaction mixture was irradiated in microwave oven (900 W with a frequency of 2450 MHz). The time of irradiation was 130 s for this particular reaction and for other derivatives time required for microwave irradiation is given in Table-1. After cooling the reaction mixture, the excess of solvent was evaporated off under vacuum. The crude product separated was filtered and recrystallized from petroleum ether to give **3a-o**.

Scheme-II: Tetramethylene-N-phenyl nitron (0.01 mol) contained in 100 mL round bottom flask were added N-4-chlorophenylmaleimide (0.01 mol) and sodium dried toluene (50 mL). The reaction mixture was refluxed on water bath. The time of reflux for this particular reaction was 12 h. The time of reflux for other derivatives is given in Table-1. After cooling the reaction mixture, the excess of solvent was evaporated off under vacuum. The crude product separated was filtered and recrystallized from petroleum ether to give **3a-o**.



R = H, CH_3, Cl X= H, NO_2, CH_3, OCH_3, Cl

Scheme-I

Analysis, %: Found: C, 65.84; H, 4.90; N, 7.27; $C_{21}H_{19}N_2O_3Cl$ requires: C, 65.88; H, 4.97; N, 7.32. IR (nujol): 1720-1710, 1610-1600, 1295-1200 cm^{-1}, ^1H NMR (400 MHz) ($CDCl_3$ + DMSO): δ 7.6-6.1 (m 9H, aromatic), δ 5.12-4.9 (d H_{6a}), δ 3.6-3.3 (d H_{3a}), δ 2.0-1.1 (m 8H, four $-CH_2$ groups).

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