Investigations on Regio- and Stereoselectivities in Cycloadditions Involving α- (3-Pyridyl)-*N*-phenylnitrone: Development of an Efficient Route to Novel Nicotine Analogs

Gurpinder Singh, M. P. S. Ishar*, Navdeep K. Girdhar and Lakhwinder Singh

Department of Pharmaceutical Sciences, Guru Nanak Dev University,
Amritsar 143 005, Punjab, India
Fax +91-183-2258820; email: mpsishar@yahoo.com
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Thermal reactions of hitherto α-(3-pyridyl)-*N*-phenylnitrone (**1**) with mono-substituted electron-rich and electron-neutral dipolarophiles are regio-, and stereo-selective (*exo*-selective), controlled by LUMO – dipole - HOMO- dipolarophile interaction, and furnish *syn*-5-substituted-3-(3-pyridyl)-isoxazolidines (**5**) in high yields. With electron deficient dipolarophiles such as acrylonitrile there is observed a loss of regioselectivity as well as stereoselectivity and the regioselectivity is reversed in reactions with methyl vinyl ketone and methyl acrylate, due to intervention of HOMO-dipole - LUMO-dipolarophile interaction, affording 4-substituted-3-(3-pyridyl)-isoxazolidines (**7**) as major products. Reactions of nitrone (**1**) with disubstituted dipolarophiles such as methyl methacrylate and ethyl coronate furnish methyl *syn*-5-methy-3-pyridyl-1-phenyl-isoxazolidine-5-carboxylate (**8**) and ethyl *anti*-5-methy-3-pyridyl-1-phenyl-isoxazolidine-4-carboxylate (**10**), respectively, in high yields. Reaction with *N*-Phenylmaleimide affords novel isoxazolidino-pyrrolidinediones bearing a 3-pyridyl moiety (**11**, **12**). A mechanistic rationalization of the obtained results in terms of electronic, steric and secondary interactions is proffered.

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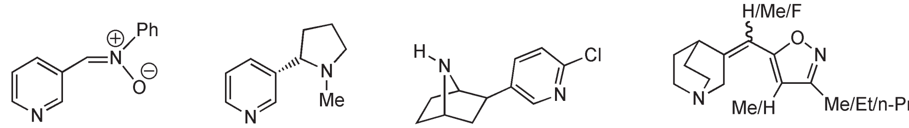
Introduction.

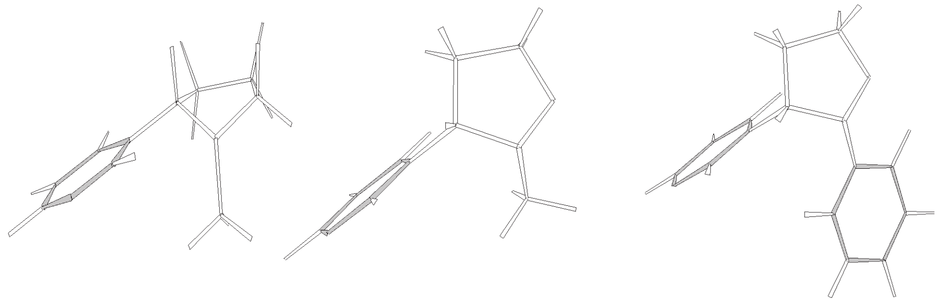
Cognizant of the well established synthetic potential of the nitrone 1,3-dipolar cycloadditions, in affording precursors/scaffolds for the synthesis of a variety of molecular frameworks [1], the chemists are showing increasing interest in synthetic [2], mechanistic/theoretical [3] investigations of 1,3-dipolar cycloadditions, involving a variedly substituted nitrones. As a part of our continuing interest in nitrone chemistry [4], we have presently investigated the regio- and stereoselectivities in the reactions of hitherto α-(3-pyridyl)-*N*-phenylnitrone (**1**) with a variety of dipolarophiles. The investigations were of particular interest because cycloadditions of the nitrone (**1**) were to furnish novel isoxazolidine analogs of nicotine (**2**). Design and development of newer ligands for nicotinic–acetylcholine-receptors (nAChRs) is drawing considerable attention due to their potential applications in the treatment of a variety of conditions such as Alzheimer's disease, Depression, Parkinson's and Tourette's syndromes, as antinociceptives (analgesics), as cognition enhancers, and for treatment of addiction to smoking [5]. The recent hectic activity in this area has been spurred by the isolation of epibatidine (**3**), a natural analog of nicotine, having useful non-opiod-antinociceptive activity [6], and by the advancement in the understanding of existence of subtypes of endogenous nAChRs with structural variation, tissues specific localization and function [5a]. Therefore, synthesis of nicotine/ epibatidine analogues, both agonists and antagonists, with improved biological/pharmacological properties, and for the characterization of receptor sub-types, is drawing considerable interest [5,7].

It is pertinent to mention here that a large number of nicotine analogs have been designed by making a rational start with nicotine itself, however, there are very few examples wherein *N*-methylpyrrolidine moiety of nicotine has been replaced with other five – membered - heterocyclic systems, though, very recently isoxazolylmethylidene-quinuclidines (**4**) have been synthesized and shown to possess broad range of affinities for nicotinic, and central muscarinic receptors [8]. Molecular modeling (MOPAC) of nicotine (**2**) and corresponding *N*-phenyl/ methyl-isoxazolidine analogs (**A**, **B**) revealed (Figure 2) that isoxazolidine moiety in these molecules shall have nearly identical stereochemical features as pyrrolidine ring in nicotine with a similar disposition of pyridyl moiety. However, the targeted analogs will possess additional spatial (steric) and binding (electronic) components, and are anticipated to possess useful pharmacological properties.



(**1**) (**2**) (**3**) (**4**)

Figure 1



(2) A B

Figure 2

Results and Discussion.

α-(3-Pyridyl)-*N*-Phenylnitrone (**1**) was obtained by reacting 3-formylpyridine with *N*-phenyhydroxylamine in dry benzene and characterized spectroscopically. Initially, the reactions of nitrone were carried out with mono-substituted dipolarophiles by refluxing equimolar solutions of the addends in dry toluene. After completion of the reaction (tlc) the residues obtained on removal of solvent under vacuum were resolved by column chromatography over silica gel. The results are summarized in Scheme 1 and Table 1.

Table 1

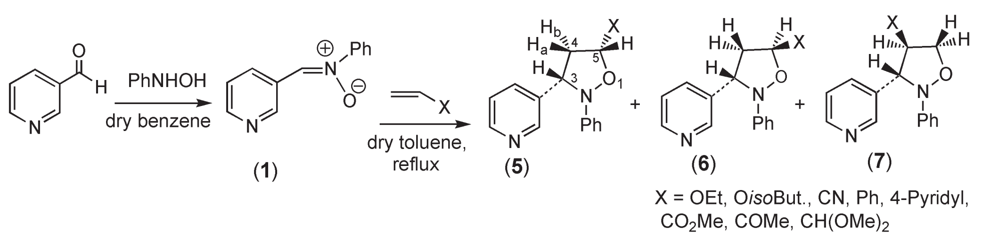
Reaction Time and Yields (%) of the Products (**5-7**)

Serial no.	X	Reaction time (h)	Yield (%)* of various products 5:6:7		
1	-OEt	30	**5a** (90)	**6a**(traces)	**7a**(--)
2	-O*iso*Butyl	12	**5b** (90)	**6b**(traces)	**7b**(--)
3	-Ph	24	**5c** (90)	**6c**(<5)	**7c**(--)
4	4-Pyridyl	24	**5d** (87)	**6d**(--)	**7d**(--)
5	-CH(OMe)$_2$	24	**5e** (75)	**6e**(--)	**7e**(--)
6	-CN	18	**5f** (40)	**6f**(30)	**7f**(20)
7	-COMe	10	**5g** (10)	**6g**(~10)	**7g**(70)
8	-CO$_2$Me	15	**5h** (15)	**6h**(15)	**7h**(60)

* Based on isolated pure products along with, in some cases, ^{1}H NMR spectral analysis of mixture fractions from column chromatography.

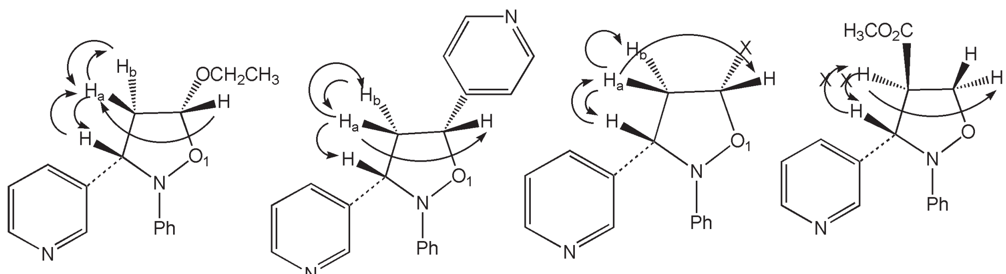
The assigned structures are based on detailed spectroscopic analysis (IR, ^{1}H NMR, ^{13}C NMR and Mass) and micro-analytical data. A comparison of the spectroscopic, in particular, NMR spectral data with the data reported for isoxazolidines obtained by 1,3-dipolar cycloadditions of nitrones to a variety of dipolarophiles [4d,9], clearly indicated that the presently obtained cycloadducts are also derived from 1,3-dipolar cycloadditions. The assigned regiochemistry of addition in (**5**) and (**6**) is based on ^{1}H NMR couplings, which clearly indicated that C4-Hs are vicinal to both C3-H and C5-H; this is also corroborated by the ^{13}C NMR chemical shifts of the various carbons of the isoxazolidines moiety [4d]. The *syn* – stereochemistry in **5** involving pyridyl group and substituent-X at C5 is based on ^{1}H NMR couplings involving C3-H, C4-H, and C5-H and follows from the premise that the *cis* - vicinal ^{1}H coupling constants are always higher than *trans* in case of isoxazolidines and related heterocycles [4d,9,10]. The ^{1}H chemical shift and coupling constant, involving C3-H, C5-H, C4-H$_a$ and C4-H$_b$, and variation in their values in going from *syn* (**5**) to *anti*-adducts (**6f**-**h**) form the bases of the assigned stereochemistry in the case of latter [4d,9,10]; the stereochemistry and relative proportion of **6g** in a mixture fraction were ascertained through a doublet at δ 5.12 (J = 6.1 Hz, C5-H) and an unresolved dd at δ 4.37 (J ~ 7.0 Hz, C3-H) *cf*. [4d]. The assigned stereochemistry in the case of **5a**,**d**,**e** is further corroborated through ^{1}H nOe enhancements observed by recording ^{1}H nOe diffrence spectra on saturating C3-H, C4-Ha, C4-Hb and C5-H resonances, and the established connectivities are shown in Figure 3. The assigned reversed regiochemistry of cycloaddition in

Scheme 1



adducts (**7 f-h**), is based on ^{1}H and ^{13}C NMR spectral data. For instance in case of (**7h**) the methylene-Hs (C5-Hs) are located as multiplet at δ 4.41-4.23 and this downfield shifted position *vis-à-vis* the ^{1}H NMR chemical shift of methylene hydrogen atoms in the regioisomeric adducts (**5**, **6**), is indicative of the attachement of methylene carbon to oxygen in **7h**; these conclusions are corroborated by the observed proton connectivities and ^{13}C NMR chemical shift assignments [4d,9,10]. Here, the assigned *trans*-arrangement of substituents at C3 and C4 is based on the lower value of coupling constant $J_{3,4}$ 5-6 Hz only [4d,9,10] and further corroborated by non observation of any mutual ^{1}H nOe enhancement in the ^{1}H nOe difference spectra recorded after saturating C3-H and C4-H resonances (Figure 3).

[11]. The regioselectivity of addition is reversed in case of reactions of the nitrone (**1**) with electron deficient dipolarophiles leading to formation of adducts **7g,h**. Surprisingly, this reversal of regioselectivity of addition, which is a consequence of change in the nature of involved frontier molecular orbital interaction, and which is generally observed in reactions of nitrones with highly electron deficient dipolarophiles like nitro-alkenes [11a-c], occurs rather early in present series as far as the electron deficiency of the involved dipolarophiles is concerned. The stereo-selectivity of addition leading to higher relative proportions of *syn*- (**5a-e**) than the corresponding *anti*-cycloadducts (**6**) can be rationalized in terms of preferred *exo*- mode of addition of nitrone in its *Z*-form [11d,12]; such *exo*-selectivity has been observed earlier also and has



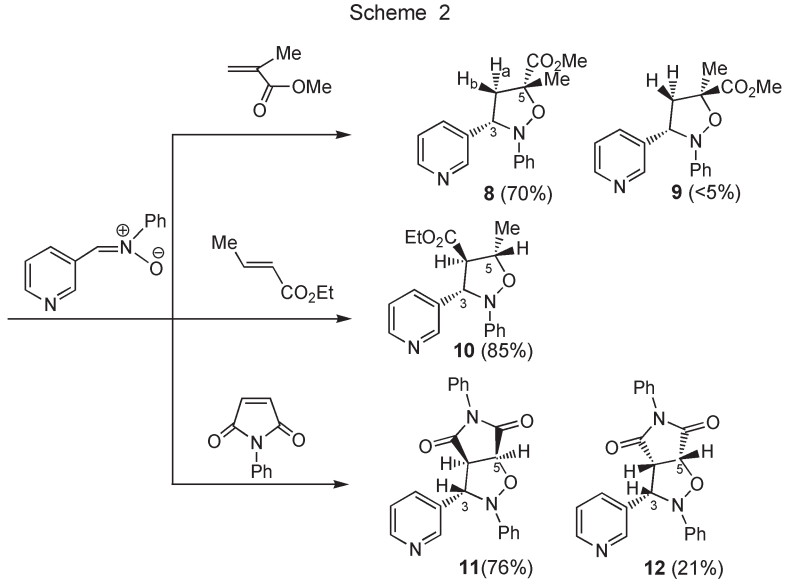
(**5a**) (**5d**) (**5e**) (**7h**)

Figure 3

The regiochemistry of addition leading to adducts (**5**) and (**6**) can be rationalized in terms of the frontier molecular orbital control of the cycloaddition, *i.e.*, in terms of LUMO (dipole) – HOMO (dipolarophiles) interaction

been attributed to steric factors [4d]. In general any significant *endo*-mode of addition is observed only in case of substituents which are capable of undergoing secondary interaction [4d,13]. However, it may be mentioned here

Scheme 2



that a variety of interactions have been invoked to explain stereoselectivities in 1,3-dipolar cycloadditions, in particular, and cycloaddition in general, though, the question of secondary orbital or secondary interaction is still far from settled and steric factors appear to play an overwhelming role [13]. Recently, preferred endo-orientation [13b,c] of alkoxy groups, even in the presence of an ester function [13c], has been reported.

Subsequently, the investigations were extended to disubstituted and cyclic dipolarophiles such as methyl methacrylate, ethyl crotonate and *N*-phenylmaleimide (Scheme 2).

Reaction of nitrone (**1**) with methyl methacrylate in refluxing toluene afforded a major product (**8**, 70 %) along with a minor product (**9**, < 5%); the latter was detected only in some mixture fractions. The stereochemistry, *i.e.*, the *cis* relationship between pyridyl moiety and ester function in **8** is based on the ^{1}H NMR chemical shifts and coupling constants values for C3-H, C4-H_a and C4-H_b. Here C4-H_a appeared as dd at δ 3.54 and its downfield shifted position *vis-à-vis* C4-H_b (dd at δ 2.39), indicated that it is *cis* to ester function [10c]. Again, lower value of coupling constant $J_{4a,3}$ 7.7 Hz as compared to $J_{4b,3}$ 8.4 Hz, indicated that C_4-H_a is *trans* to C_3-H, which is also corroborated by comparison of the overall ^{1}H and ^{13}C NMR spectral data with the data reported for cycloadducts derived from addition of various nitrones to methyl methacrylate [4d,10c]. The *cis* relationship between C3-H, C4-H_b and C5-Me is ascertained through spatial proximity established by recording ^{1}H nOe difference spectra after saturating C3-H and C5-Me resonances (Figure 4). The other isomer (**9**) could be detected only in trace amount in some column fractions.

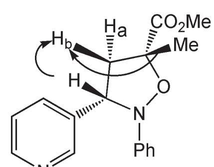


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Figure 4

The obtained major mode of addition can be rationalized as *exo*-addition as far as ester function is concerned with nitrone reacting in *Z* - form (**C**) or *endo*-orientation of ester function with nitrone reacting in *E*-form (**D**) *cf.* [4d]; preferred endo-selectivity of α-methyl groups for steric reasons has also been observed in the case of some Diels-Alder reactions [13d].

A similar reaction of nitrone (**1**) with ethyl crotonate afforded a single product, which has been characterized as cycloadduct (**10**) by comparison of the spectroscopic data with the data reported for cycloadducts derived from addition of nitrones to crotonates [4d,10f,g]. The assigned regiochemistry of addition is easily discerned from the chemical shift value of C5-H (δ 4.39); the C5-H resonance could be easily identified from its multiplicity (dq). Here the *trans* - relationship between C3-H and C4-H is based on $J_{3,4}$ = 6.7 Hz as it is still lower than the $J_{4,5}$ = 8.9 Hz; the latter hydrogens are anticipated to be *trans* as a consequence of concerted cycloaddition to *trans*-crotonate *cf.* [10f,g]. The assigned *trans* stereochemistry is further corroborated by ^{1}H nOe investigations (Figure 5). Though, the regiochemistry of addition was anticipated in the light of literature reports [4d,1b,11], however, the important aspect of the present results is obtained complete regio- and stereo-selectivity, which can be rationalized in terms of addition of nitrone in *Z* - form with ester moiety being *endo*-oriented in the transition state (approach **E**) for steric reasons (Figure 5).

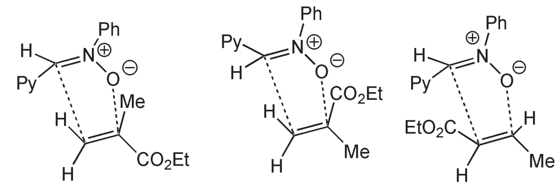

Figure 5

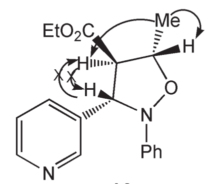

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Figure 6

Similar, reaction of nitrone (**1**) with *N*-phenylmaleimide under identical conditions afforded two compounds (**11**) and (**12**). The major compound (**11**) displayed, *interalia*, a 1H singlet at δ 5.71, which was attributed to C3-H and signified its *trans* – relationship with C4-H; such lack of any observable coupling between *trans*- vicinal-hydrogen atoms in case of isoxazolidines, particularly, in case of rigid systems derived from addition of nitrones to cyclic-dipolarophiles has precedent [4d]. Both C4-H and C5-H were present as 1H doublets at δ 3.91 and δ 5.30, respectively, displaying a mutual splitting of 7.5 Hz. The minor cycloadduct (**12**) on the other hand displayed C3-H resonance as a doublet (1H, J = 8.7 Hz), C5-H as a doublet at δ 4.84 (1H, J = 9.9 Hz) and C4 - H as an unresolved double doublet at δ 3.92. Mechanistically, the compound (**11**) can be described as the *endo* – and **12** as the corresponding *exo* –adduct derived from addition of nitrone in Z - form.

Conclusion.

In summary the *regio*- and *stereo*-selectivities in cycloadditions of hitherto α-(3-pyridyl)-*N*-phenylnitrone have been investigated. The cycloadditions have provided an easy access to a variety of substituted mono- and bicyclic - isoxazolidine analogs of nicotine, which are anticipated to display useful biological activities.

EXPERIMENTAL

Bruker AC-200 (200 MHz) and JEOL-AL-300FT NMR spectrometers were used to record ^{1}H NMR, and ^{13}C NMR (50 MHz) spectra in $CDCl_3$ as solvent. Chemical shifts (δ) are reported as downfield displacements from tetramethylsilane (TMS) used as internal standard. IR spectra were recorded on Shimadzu DR-2001 FT-IR spectrophotometer as thin film with chloroform ($CHCl_3$) or as Potassium bromide (KBr) pellets. Mass spectra, EI and ESI-methods, were recorded on Shimadzu GCMS-QP-2000A and Bruker Daltonics Esquire 300 mass spectrometers, respectively. Elemental Analysis was carried out on a Perkin-Elmer 240C elemental analyzer and are reported in percent atomic abundance. All melting points are uncorrected and measured in open glass-capillaries on a Precision (make) MP-D digital melting point apparatus.

C-(3-Pyridyl)-*N*-phenylnitrone (**1**).

3-Formylpyridine (3.0 g, 2.8 mmol) was dissolved in dry benzene (30 ml) and to the clear solution was added *N*-phenylhydroxylamine hydrochloride (4.08 g, 2.8 mmol) and the contents were allowed to stand at room temperature. After 30 minutes nitrone (**1**) separated out as a light yellow solid, which was collected by filtration (5.2 g, 95%); mp 88-89 °C (benzene: hexane, 1:1); ir (potassium bromide): 3065, 3019, 2925, 1591, 1555, 1485, 1460, 1424, 1411, 1216 cm^{-1}; ^{1}H nmr (duteriochloroform): δ 7.42 -7.52 (m, 4H, Ar-Hs & 5-H), 7.81(m, 2H, Ar-Hs), 8.0(s, 1H, α–H), 8.65(d, 1H, J = 4.2 Hz, 6-H), 9.07(s, 1H, 2-H), 9.27(d, 1H, J = 8.1 Hz, 4-H); ^{13}C nmr (duteriochloroform): δ 121.31(CH), 123.52(C-5), 127.32(C-α), 128.97(CH), 130.12(CH), 131.18(C-3), 135.14(C-4), 148.26(C-6), 149.93(q), 151.58(C-2); EI MS: m/z (rel. int.) = 199(M$^+$+1, 5), 198(M$^+$, 25), 197(M$^+$-1,12), 182(40), 91(90), 78(30), 77(100).

Anal. Calcd. for $C_{12}H_{10}N_2O$ (198): C, 72.71; H, 5.08; N, 14.13. Found: C, 72.63; H, 5.00; N, 14.02.

General Procedure for the Reaction of Nitrone (**1**) with Various Dipolarophiles.

To a solution of nitrone (300 mg) in dry toluene (50 ml) was added the dipolarophile (1 molar equivalent) and the solution was refluxed with stirring. After the completion of the reaction (tlc), the solvent was removed under reduced pressure. The products were purified by column chromatography (silica gel 60-120 mesh, 20 g, column packed in hexane). The reported yields were based on isolated pure products and the relative proportions were determined in mixtures by ^{1}H NMR spectroscopy.

Reaction of Nitrone (**1**) with Ethyl Vinyl Ether.

Reaction of nitrone (**1**, 300 mg)) with ethyl vinyl ether (109 mg) and column chromatography of the residue (hexane:ethyl acetate 9:1 eluent) afforded syn-5-ethoxy-2-phenyl-3-(3-pyridyl)-isoxazolidine (**5a**) as light brown viscous oil (370 mg); ir (chloroform): 3032, 2976, 1599, 1489, 1427, 1326, 1271, 1201 cm^{-1}; ^{1}H nmr (duteriochloroform): δ 1.28(t, 3H, J = 7.1 Hz, CH_3), 2.33(dd, 1H, J_{gem} = 11.2 Hz & J = 5.5 Hz, 4-Hb), 3.00(ddd, 1H, J_{gem} = 11.2 & J = 9.8, 5.8 Hz, 4-Ha), 3.59(qd, 1H, J_{gem} = 11.7 & J = 7.1 Hz, OCH_2), 3.98(qd, 1H, J_{gem} = 11.7 & J = 7.1 Hz, OCH_2), 4.38(dd, 1H, J = 9.8 & 5.5 Hz, 3-H), 5.38(d, 1H, J = 5.8 Hz, 5-H), 6.87-6.98 (m, 3H, Ar-Hs), 7.14-7.40 (m, 3H, Ar-Hs & 5′-H), 7.97(d, 1H, J = 7.8 Hz, 4′-H), 8.53(d, 1H, J = 4.1 Hz, 6′-H), 8.63 (s, 1H, 2′-H); ^{13}C nmr (duteriochloroform): δ 14.72(CH_3), 45.21(C-4), 63.04(OCH2), 65.92(C-3), 100.32(C-5), 115.86 (CH), 122.31(CH), 123.39(C-5′), 128.20(CH), 134.94(C-4′), 137.04(C-3′), 148.24 (q), 148.29 & 149.54(C-2′ & C-6′); EI-MS: m/z (rel. int.) = 270(M$^+$, 6), 183(30), 182(30), 181(25), 162(55), 134(55), 93(45), 91(40), 77(100).

Anal. Calcd. for $C_{16}H_{18}N_2O_2$ (270): C, 71.09; H, 6.71; N, 10.36. Found: C, 70.97; H, 6.75; N, 10.25.

Reaction of Nitrone (**1**) with Isobutyl Vinyl Ether.

Reaction of nitrone (**1**, 300 mg) with isobutyl vinyl ether (152 mg) and column chromatography of the residue (hexane:ethyl acetate 9:1 eluent) afforded syn-5-isobutoxy-2-phenyl-3-(3-pyridyl)-isoxazolidine (**5b**) as light yellow viscous oil (410 mg); ir (chloroform): 3080(sh), 3019, 2961, 2874, 1599, 1489, 1428, 1216 cm^{-1}; ^{1}H nmr (duteriochloroform): δ 0.93 (d, 6H, J = 6.7 Hz, 2 × CH_3). 1.76-2.19(m, 1H, CH), 2.35(ddd, 1H, J_{gem} = 12.2 Hz & J = 5.1 &1.2 Hz, 4-Hb), 2.99(ddd, 1H, J_{gem} = 12.2 & J 9.9 & 5.8 Hz, 4-Ha), 3.27(dd, 1H, J_{gem} = 9.2 & J = 6.6 Hz, OCH_2), 3.69(dd, 1H, J_{gem} = 9.2 & J = 6.7 Hz, OCH_2), 4.42(dd, J = 9.9 & 5.1 Hz, 3-H), 5.36(dd, 1H, J = 5.8 & 1.2 Hz, 5-H), 6.87-6.94(m, 3H, Ar-Hs), 7.15-7.32 (m, 3H, Ar-Hs & 5′-H), 7.97(dt, 1H, J = 6.0 & ~1.8 Hz, 4′-H), 8.54(dd, 1H, J = 4.7 & 1.5 Hz, 6′-H), 8.65(d, 1H, J = 1.8 Hz, 2′-H); ^{13}C nmr (duteriochloroform): δ 19.35(CH_3), 28.35(CH), 45.37(C-4), 66.05(C-3), 74.78(OCH_2), 101.16(C-5), 116.04(CH), 122.50 (CH), 123.66(C-5′), 128.60(CH), 135.12(C-4′), 137.62(C-3′), 148.71(overlapping C-6′ & q arom.), 150.10 (C-2′); EI MS: m/z (rel. int.) = 300(M$^+$+2, 0.5), 299(M$^+$+1,1.5), 298(M$^+$, 45), 190(30), 134(100).

Anal. Calcd. for $C_{18}H_{22}N_2O_2$ (298) : C, 72.46; H, 7.43; N, 9.39. Found: C, 72.36; H, 7.31; N, 9.26.

Reaction of Nitrone (**1**) with Styrene.

Reaction of nitrone (**1**, 300 mg)) with styrene (158 mg) and column chromatography of the residue (hexane:ethyl acetate 9:1 eluent) afforded syn-2,5-diphenyl-3-(3-pyridyl)-isoxazolidine (**5c**) as light brown viscous oil (415 mg); ir (chloroform): 3081, 3019, 1598, 1488, 1426, 1362, 1220 cm^{-1}; ^{1}H nmr (duteriochloroform): δ 2.48(ddd, 1H, J_{gem} = 12.2 & J = 9.5 & 7.6 Hz, 4-Ha), 3.25 (ddd, 1H, J_{gem} = 12.2 & J = 8.1 , 6.0 Hz, 4-Hb), 5.01(dd, 1H, J = 8.1 & 7.6 & Hz, 3-H), 5.23(dd, 1H, J = 9.5 & 6.0 Hz, 5-H), 6.97-7.10(m, 3H, Ar-Hs), 7.18-7.42(m, 8H, Ar-Hs and 5′-H), 7.97(d, 1H, J = 7.8 Hz, 4′-H), 8.59(d, 1H, J = 3.6 Hz, 6′-H), 8.77(bs, 1H, 2′-H); ^{13}C nmr (duteriochloroform): δ 48.06(C-4), 66.95(C-3), 80.53(C-5), 114.01(CH), 121.85(CH), 123.86(C-5′), 126.79(CH), 128.66(CH), 128.73(CH), 129.17(CH), 134.16(C-4′), 137.51(q), 138.63(C-3′), 148.05(q), 148.52(C-6′), 151.97(C-2′); EI MS m/z(rel. int.) = 304(M$^+$+2, 1), 303(M$^+$+1, 3.5), 302(M+, 70), 194(35), 183(30), 105(40), 91(60), 77(100).

Anal. Calcd. for $C_{20}H_{18}N_2O$ (302) : C, 79.44; H, 6.00; N, 9.26. Found: C, 79.42; H, 5.92; N, 9.17.

Reaction of Nitrone (**1**) with 4-Vinyl Pyridine**.**

Reaction of nitrone (**1**, 300 mg)) with 4-vinylpyridine (160 mg) and column chromatography of the residue (hexane:ethyl acetate 7:3 eluent) afforded syn-2-phenyl-3-(3-pyridyl)-5-(4-pyridyl)-isoxazolidine (**5d**) as light brown viscous oil (400 mg); ir (chloroform): 3065, 3055, 2924, 1599, 1559, 1541, 1488, 1418 cm^{-1}; ^{1}H nmr (duteriochloroform): δ = 2.35-2.21(m, 1H, 4-Hb), 3.20(td, 1H, J_{gem} = 11.6 & J = 7.5 Hz, 4-Ha), 4.85(unresolved dd, 1H, J ~ 7.5 Hz, 3-H), 5.14(unresolved dd,1H, J ~7.7 Hz, 5-H), 6.85-6.95(m, 3H, Ar-Hs), 7.21-7.09(m, 5H, Ar-Hs & 5′-H, 3′′-H, 5′′-Hs), 7.89(dd, 1H, J = 6.4 & 1.9 Hz, 4′-H), 8.43-8.50(m, 3H, 2′′-H, 6′-H & 6′′-H), 8.58 (bs, 1H, 2′-H); ^{13}C nmr (duteriochloroform): δ 47.21(C-4), 66.40(C-3), 78.22(C-5), 114.39(CH), 121.01 (CH), 122.71(C-3′′ & C-5′′), 123.73(C-5′), 129.07(CH), 134.03(C-4′), 137.58(C-3′), 147.59(C-4′′), 148.24(q), 149.05(C-6′), 149.83(C-2′′ & C-6′′), 151.05(C-2′); EI MS m/z(rel. int.) = 303(M^+, 5), 302(M^+-1, 15), 301(M^+-2, 78), 283(30), 171(90), 112(70), 94(30), 83(55), 71(100), 70(90).

Anal. Calcd. for $C_{19}H_{17}N_3O$ (303): C, 75.23; H, 5.65; N, 13.85. Found: C, 75.14; H, 5.57; N, 13.78.

Reaction of Nitrone (**1**) with Acroleindimethylacetal.

Reaction of nitrone (**1**, 300 mg) with acroleindimethylacetal (155 mg) and column chromatography of the residue (hexane:ethyl acetate 9:1 eluent) afforded syn-5-dimethoxymethyl-2-phenyl-3-(3-pyridyl)-isoxazolidine (**5e**) as brown viscous oil (340 mg); ir (chloroform): 3019, 1600, 1521, 1424, 1216 cm^{-1}; ^{1}H nmr (duteriochloroform): δ 2.35-2.16(m, 1H, 4-Hb), 2.60-2.80(m, 1H, 4-Ha), 3.26(s, 3H, OCH_3), 3.38(s, 3H, OCH_3), 4.22-4.30(m, 2H, 5-H & OCH), 4.71(dd, 1H, J = 7.9 & 5.9 Hz, 3-H), 6.93-6.83(m, 3H, Ar-Hs), 7.11-7.19(m, 3H, Ar-Hs & 5-H), 7.79(d, 1H, J = 7.8 Hz, 4′-H), 8.44(d, 1H, J = 4.2 Hz, 6′-H), 8.60 (bs, 1H, 2′-H); ^{13}C nmr (duteriochloroform): δ 40.37(C-4). 54.09(OCH_3), 54.70(OCH_3), 67.53(C-3), 78.11(C-5), 104.16[*C*H-$(OCH_3)_3$], 114.64 (CH), 121.14(CH), 123.46(C-5′), 128.82(CH), 134.37(C-4′), 137.96(C-3′), 149.26(q), 150.49 (C-6′), 150.93(C-2′); EIMS m/z(rel. int.) = 302(M^++2, 2), 301(M^++1, 10), 300(M^+, 40), 183(40), 182(43), 181 (48), 120(25), 104(30).

Anal. Calcd. for $C_{17}H_{20}N_2O_3$ (300): C, 67.98; H, 6.71; N, 9.33. Found C, 67.86; H, 6.65; N, 9.28.

Reaction of Nitrone (**1**) with Acrylonitrile.

Reaction of nitrone (**1**, 300 mg)) with acrylonitrile (81 mg) and column chromatography of the residue (hexane:ethyl acetate 95:5 eluent) afforded, in order of elution: *syn*-2-phenyl-3-(3-pyridyl)-isoxazolidine-5-carbonitrile (**5f**) as light brown viscous oil (38 mg); ir (chloroform): 3043, 2922, 2246, 1596, 1489, 1453.9, 1427, 1322, 1261 cm^{-1}; ^{1}H nmr (duteriochloroform): δ 2.58(ddd, J_{gem} = 12.9 and J = 3.4 & 5.5 Hz, 4-Hb), 3.17(unresolved ddd, J_{gem} = 12.9 & J ~ 9.0 Hz 4-Ha), 4.90(dd, J = 8.9 & 5.5 Hz, 5′-H), 4.98(dd, J = 9.3 & 3.4 Hz, 3-H), 6.94-7.09(m, 3H, Ar-Hs), 7.21-7.39(m, 3H, Ar-Hs & 5-H), 7.91(d, J = 8.1 Hz, 4′-H), 8.32-8.55(m, 2H, 2′-H & 6′-H); ^{13}C nmr (duteriochloroform): δ 44.03(C-4′), 63.96(C-5′), 69.13(C-3′), 115.86(CH), 117.23 (CN), 123.80(CH), 124.47(C-5′), 128.95(CH), 134.76(C-4′), 135.52(C-3′), 148.02(q), 148.57(C-6′), 149.63(C-2′); EI MS m/z(rel. int.) = 252(M^++1, 5), 251(M^+, 25), 183(20), 182(40), 181(42), 104(25), 93(35), 91(60), 77(100).

Anal. Calcd. for $C_{15}H_{13}N_3O$ (251) : C, 71.70; H, 5.21; N, 16.72. Found C, 71.59; H, 5.18; N, 16.6.

A mixture (~ 1:1) of **5f** with corresponding *anti*- isomer (**6f**, 230 mg), Critical ^{1}H and ^{13}C nmr features of **6f:** ^{1}H nmr (duteriochloroform): δ 2.67-2.77(m, 4-Hb), 2.90-3.06(m, 4-Ha), 4.59(dd, 1H, J = 9.1 & 5.5 Hz, 5-H), 5.08(dd, 1H, J = 8.2 & 3.4 Hz, 3-H), 7.86(d, J = 8.1 Hz, 4′-H); ^{13}C nmr (duteriochloroform): δ 43.45(C-4), 65.02(C-5), 68.60(C-3), 115.61(CH), 117.78(CN), 122.21(CH), 124.09(C-5′), 128.18(CH), 134.83(C-4′), 135.87(C-3′), 148.53(q), 149.25(C-6′), 151.35(C-2′). *anti*-2-phenyl-3-(3-pyridyl)-isoxazolidine**-**4-carbonitrile (**7f**) as yellowish viscous mass (75 mg); ir (chloroform): 3025, 2238, 1599, 1490, 1465, 1426, 1386, 1320, 1265 cm^{-1}; ^{1}H nmr (duteriochloroform): δ 3.46(. ddd, 1H, J = 5.8 ,7.1 & 8.5 Hz, 4-H)**,** 4.32(dd, 1H, J_{gem} = 10.4 & J 7.1 Hz, 5-H), 4.35(dd, 1H, J_{gem} = 10.4 & J = 8.5 Hz, 5-H), 4.93(d, 1H, J = 5.8 Hz, 3-H), 7.10-6.93(m, 3H, Ar-Hs), 7.20-7.38(m, 3H, Ar-Hs and 5′-H), 7.82(d, 1H, J = 7.9 Hz, 4′-H), 8.50-8.65 (br, 2H, 2′-H & 6′-H); ^{13}C nmr (duteriochloroform): δ 44.71(C-4). 66.37(C-5), 71.52(C-3), 115.68(CH), 117.18 (CN), 123.80(C-5′), 121.53 (CH), 129.20(CH), 134.19(C-4′), 135.04 (C-3′), 147.85(q), 149.46 (C-6′), 149.63(C-2′); EIMS m/z (rel. int.) = 251(M^+, 20,), 182(40), 144(25), 92(20), 91(67), 77(100).

Anal. Calcd. for $C_{15}H_{13}N_3O$ (251): C, 71.70; H, 5.21; N, 16.72. Found C, 71.62; H, 5.12; N, 16.59.

Reaction of Nitrone (**1**) with Methyl Vinyl Ketone.

Reaction of nitrone (**1**, 300 mg)) with methyl vinyl ketone (107 mg) and column chromatography of the residue (hexane:ethyl acetate 9:1 eluent) afforded, in order of elution: *syn*-5-acetyl-2-phenyl-3-(3-pyridyl)-isoxazolidine (**5g**) as yellow viscous oil (~60 mg); ir (chloroform): 3019, 1718, 1600, 1522, 1476, 1423, 1216 cm^{-1}; ^{1}H nmr (duteriochloroform): δ = 2.34(s, 3H, CH_3). 2.63(dt, 1H, J_{gem} = 12.7 & J = 5.1 Hz, 4-Hb), 2.98(ddd, J_{gem} = 12.7 & *J* = 9.2, 7.0 Hz, 4-Ha), 4.58(dd, 1H, J = 9.2 & 5.1 Hz, 3-H), 4.69(dd, 1H, J = 7.0 & 5.1 Hz, 5-H), 6.80-7.03(m, 3H, Ar-Hs), 7.15-7.40(m, 3H, Ar-Hs & 5′-H), 7.74(br d, 1H, J = 8.0 Hz, 4′-H), 8.50-8.62 (br, 2H, 2′-H & 6′-H). ^{13}C nmr (duteriochloroform): δ 25.67(CH_3). 40.12(C-4), 67.15(C-3), 81.54(C-5), 116.67(CH), 123.64(CH), 126.57(C-5′), 128.83(CH), 134.31(C-4′), 138.53(C-3′), 148.59(q), 149.18(C-6′), 151.53(C-2′), 201.35 (C=O). EI MS m/z(rel. int.) = 270(M^++2, 2), 269(M^++1, 4), 268(M^+, 12), 187(10), 170(15), 111(65), 71(100).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$ (268) : C, 71.62; H, 6.01; N, 10.44. Found C, 71.55; H, 5.94, N, 10.31.

anti-4-Acetyl-2-phenyl-3-(3-pyridyl)-isoxazolidine (**7g**) as yellowish viscous material (285 mg). ir (chloroform): 3019, 1716, 1598, 1521, 1489, 1428, 1215 cm^{-1}. ^{1}H nmr (duteriochloroform): δ 2.16(s, 3H, CH_3), 3.64(ddd, 1H, J = 8.4, 7.5 & 5.7 Hz, 4-H), 4.14(dd, 1H, J_{gem} = 8.1 & J = 7.5 Hz, 5-H), 4.45(dd, 1H, J_{gem} = 8.1 & J = 8.4 Hz, 5-H), 5.06(d, 1H, J = 5.7 Hz, 3-H), 6.91-6.98(m, 3H, Ar-Hs), 7.15-7.33(m, 3H, Ar-Hs & 5′-H), 7.84(dt, 1H, J = 8.7 & ~1.4 Hz, 4′-H), 8.55(dd, 1H, J = 4.6 & 1.2 Hz, 6′-H), 8.69(d, 1H, J = 1.4 Hz, 2′-H); ^{13}C nmr (duteriochloroform): δ 29.56(CH_3), 66.75(C-4), 68.40(overlapping C-3 & C-5 resolved by DEPT), 115.10(CH), 123.80(CH), 126.67(C-5′), 128.95(CH), 134.42(C-4′), 137.15(C-3′), 148.32(C-6′), 149.16(C-2′), 149.94(q), 203.11(C=O); EI MS m/z(rel. int.) = 270(M^++2, 2), 269(M^++1, 7), 268(M^+, 13), 169(100).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$ (268): C, 71.62; H, 6.01; N, 10.44. Found C, 71.49; H, 5.96; N, 10.34.

Reaction of Nitrone (**1**) with Methyl Acrylate.

Reaction of nitrone (**1**, 300 mg)) with methyl acrylate (131 mg) and column chromatography of the residue (hexane:ethyl acetate 9:1 eluent) afforded a mixture (1:1) of methyl *syn/anti*-2-phenyl-3-(3-pyridyl)-isoxazolidine-5-carboxylate (**5h** & **6h**) as brownish viscous material (130 mg); ir (chloroform): 2984, 1740, 1605, 1581, 1496, 1474, 1421, 1414, 1316, 1315, 1224, 1211 cm^{-1}. ^1H nmr (duteriochloroform): δ 2.38(ddd, 1H, J = 12.7, 5.2 Hz & 2.0 Hz, 4-Hb in **5h**), 2.50-2.80(m, 2H, 4-Ha and 4-Hb in **6h**), 2.98(unresolved ddd, 1H, J = 12.7 & ~7.2 Hz , **4-Ha** in **5h**), 3.67 & 3.73(singlets 3H each, $-OCH_3$ in **5h** & **6h**), 4.52(unresolved dd, 1H, J ~ 7.4 Hz, 3-H in **6h**), 4.72(dd, 1H, J = 8.4 Hz, 5.2, 3-H in **5h**), 5.16(dd, 1H, J = 7.9 & 2.0 Hz, 5-H in **5h**), 5.25 (br d, 1H, J = 6.8 Hz, 5-H in **6h**), 6.90-7.00(m, 6H, Ar-Hs in, **5h** & **6h**), 7.15-7.40(m, 6H, Ar-Hs & 5′-H, in **5h** & **6h**), 7.84(br d, 2H, J ~ 7.9 Hz, 4′-H, in **5h** & **6h**), 8.70-8.77(overlapping ds, 2H, 6′-H in **5h** & **6h**), 8.97 (br s, 2H, 2′-H in 5h & 6h). ^{13}C nmr (duteriochloroform): δ 41.57 & 41.69 (C-4 in **5h** and **6h**), 51.86(OMe in **6h**), 52.76(OMe in **5h**), 66.67 (C-3 in **5h**), 67.30(C-3 in **6h**), 75.37(C-5 in **5h**), 75.75(C-5 in **6h**), 115.66, 116.15, 123.11, 124.75, 126.50, 126.63, 128.63, 129.18, 134.38, 134.57, 135.91, 136.90, 148.31, 148.97, 149.67, 150.77, 151.29, 151.86, 170.49 & 169.40 (ester C=O in **5h** & **6h**); ESI-MS m/z = 324(M + K)$^+$. Methyl a*nti*-2-phenyl-3-(3-pyridyl)-isoxazolidine-4carboxylate (**7h**) as light yellow oil (260 mg); ir (chloroform): 3020, 1739, 1599, 1521, 1426, 1216cm^{-1}; ^1H nmr (duteriochloroform): δ 3.47-3.57(m, 1H, 4-H), 3.68(s, 3H, OCH_3), 4.23-4.41 (m, 2H, 5-Hs), 5.05(d, 1H, J = 5.5 Hz, 3-H), 6.92-7.02(m, 3H, Ar-Hs), 7.18-7.42(m, 3H. Ar-Hs & 5′-H), 7.87(d, 1H, J = 7.8 Hz, 4′-H), 8.71(d, 1H, J = 4.3 Hz, 6′-H), 8.97(s, 1H, 2′-H); ^{13}C nmr (duteriochloroform): δ 52.55(OMe), 56.05(C-4), 68.75(C-3), 69.61(C-5), 115.03(CH), 123.78(CH), 126.49(C-5′), 128.93(CH), 134.38(C-4′), 136.50(C-3′), 148.30(q), 149.12 (C-6′), 149.96 (C-2′), 170.84(C=O); EI MS m/z(rel. int.) = 284(M^+, 10), 283(M^+-1, 30), 169(90), 111(75), 94(40), 71(100), 70(90).

Anal. Calcd. For $C_{16}H_{16}N_2O_3$ (284): C, 67.59; H, 5.67; N, 9.85. Found C, 67.66; H, 5.69; N, 9.74.

Reaction of Nitrone (**1**) with Methyl Methacrylate.

Reaction of nitrone (**1**, 300 mg)) with methyl methacrylate (152 mg) and column chromatography of the residue (hexane:ethyl acetate, 90:10 eluent) afforded in order of elution methyl *syn*-5-methyl-2-phenyl-3-(3-pyridyl)-isoxazolidine-5-carboxylate (**8**) as light brown viscous oil (295 mg); ir (chloroform): 3059, 3034, 2995, 2952, 1735, 1597, 1489, 1454, 1429, 1281, 1203 cm^{-1}; ^1H nmr (duteriochloroform): δ 1.74(s, 3H, 5-Me), 2.39(dd, 1H, J_{gem} =12.2 & J = 8.4 Hz, 4-Hb), 3.54(dd, 1H, J_{gem} = 12.2 & J = 7.7 Hz, 4-Ha), 3.67(s, 3H, OCH_3), 4.98(dd, 1H, J = 8.4 &7.7 Hz, 3-H), 6.95-7.07(m, 3H, Ar-Hs), 7.27(t, 2H, J = 7.6 Hz, Ar.-Hs), 7.40(dd, 1H, J = 8.1 & 5.3 Hz, 5′-H), 7.94(d, 1H, J = 7.9 Hz, 4′-H), 8.64(d, 1H, J = 3.8 Hz, 6′-H), 8.78(s, 1H, 2′-H); ^{13}C nmr (duteriochloroform): δ 22.21(CH_3), 48.96(C-4), 52.32(OCH_3), 67.06(C-3), 83.39(C-5), 114.49(CH), 121.79(CH), 123.94(C-5′), 128.52(CH), 134.53(C-3′), 147.87(q), 148.60(C-6′), 150.44(C-2′), 172.97(ester C=O); EI MS m/z(rel. int.) = 300(M^++2, 5), 299(M^++1, 10), 298(M^+, 35), 181(30), 130(30), 106(50), 91(100), 77(95).

Anal. Calcd. for $C_{17}H_{18}N_2O_3$ (298): C, 68.44; H, 6.08; N, 9.39. Found C, 68.32; H, 5.97; N, 9.29.

A 2:1 mixture of **8** with methyl *anti*-5-methyl-2-phenyl-3-(3-pyridyl)-isoxazolidine-5-carboxylate (**9,** 68 mg); Critical ^{13}C nmr spectral features of **9**: δ 174.01(C = O), 148.57(C-2′), 135.06(C-3′), 123.89(C-5′), 82.04(C-5), 52.64(OCH_3), 48.20(C-4), 22.70(CH_3).

Reaction of Nitrone (**1**) with Ethyl Crotonate.

Reaction of nitrone (**1**, 300 mg) with ethyl crotonate (170 mg) and column chromatography of the residue (hexane:ethyl acetate 9:1 eluent) afforded ethyl *anti*-5-methyl-2-phenyl-3-(3-pyridyl)-isoxazolidine-4-carboxylate (**10**) as yellow oil (400 mg); ir (chloroform): 3020, 1732, 1598, 1488, 1429, 1216 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.22 (t, 3H, J = 7.2 Hz, CH_3), 1.50(d, 3H, J = 5.9 Hz, 5-CH_3), 3.08(dd, 1H, J = 8.9 & 6.7 Hz, 4-H), 4.14(q, 2H, J = 7.1 Hz, OCH_2), 4.39 (dq, 1H, J = 8.9 & 5.9 Hz, 5-H), 5.18(d, 1H, J = 6.7 Hz, 3-H), 6.87-6.94(m, 3H, Ar-Hs), 7.10-7.32(m, 3H, Ar-Hs & 5′-H), 7.90(d, 1H, J = 7.9 Hz, 4′-H), 8.53(d, 1H, J = 4.1 Hz, 6′-H), 8.71(s, 1H, 2′-H). ^{13}C nmr (duteriochloroform): δ 13.98(CH_3), 17.36(C5-CH_3), 61.54(-OCH_2), 65.12(C-4), 71.07(C-3), 76.60(C-5), 115.78(CH), 121.84(CH), 123.90(C-5′), 129.02 (CH), 134.48(C-4′), 137.76(C-3′), 147.72(q), 149.15(C-6′), 151.05(C-2′), 169.75(C=O). ESI MS m/z = 352(M + K)$^+$.

Anal. Calcd. for: $C_{18}H_{20}N_2O_3$ (312): C, 69.21; H, 6.45; N, 8.97. Found C, 69.15; H, 6.40; N, 8.89.

Reaction of Nitrone (**1**) with *N*-Phenylmaleimide.

Reaction of nitrone (**1**, 300 mg) with *N*-phenylmaleimide (263 mg) and column chromatography of the residue (hexane:ethyl acetate 90:10 to 85:15, eluent) afforded: *endo*-cycloadduct (**11**) as brown solid (430 mg); mp 183-185 °C (diethyl ether). ir (potassium bromide): 3060, 2962, 1712, 1592, 1498, 1488, 1453, 1425, 1387, 1327, 1243 cm^{-1}; ^1H nmr (duteriochloroform): δ 3.91(d, 1H, J = 7.5 Hz, 4-H), 5.03(d, 1H, J = 7.5 Hz, 5-H), 5.71(s, 1H, 3-H), 6.54(dd, 2H, J = 6.9 & 1.8 Hz, Ar-Hs), 6.97(t, 1H, J = 7.2 Hz, Ar-H), 7.12(d, 2H, J = 7.5 Hz, Ar-Hs), 7.19-7.28(m. 6H, Ar-Hs & 5′-H), 7.56(d, 1H, J = 8.2 Hz, 4′-H), 8.55(broad, 1H, 6′-H), 8.75(broad, 1H, 2′-H); ^{13}C nmr (duteriochloroform): δ 56.65(C-4), 67.60(C-3), 77.06(C-5), 114.47(CH), 122.48(CH), 123.21(C-5′), 125.99(CH), 128.90(CH), 129.40(C-4′), 130.74(q), 134.29(C-4′), 137.51(C-3′), 148.20 (q aromatic), 148.16(C-6′), 149.45(C-2′), 172.01(C=O), 173.41(C=O); (ESI) m/z = 394(M + Na)$^+$.

Anal. Calcd. for $C_{22}H_{17}N_3O_3$ (371): C, 71.15; H, 4.61; N, 11.31. Found C, 71.02; H, 4.57; N, 11.20.

Exo-cycloadduct (**12**) as light brown solid, (120 mg); mp 215-217 °C (diethyl ether). ir (potassium bromide): 3064, 2922, 1700, 1598, 1541, 1498, 1384, 1315 cm^{-1}; ^1H nmr (duteriochloroform): δ 3.92(dd, 1H, J = 9.9 & 8.7 Hz, 4-H), 4.84(d, 1H, J = 9.9 Hz, 5-H), 5.64(d, 1H, J = 8.7 Hz, 3-H), 6.63-6.73(m, 3H, Ar-Hs), 7.10-7.27(m, 4H, Ar-Hs), 7.41-7.48(m, 4H, Ar-Hs & 5′-H), 7.88(d, 1H, J = 7.8 Hz, 4′-H), 8.45(d, 1H, J = 4.0 Hz, 6′-H), 8.61 (br, 1H, 2′-H). (ESI) m/z = 394 (M + Na)$^+$.

Anal. Calcd. for $C_{22}H_{17}N_3O_3$ (371): C, 71.15, H, 4.61, N, 11.31. Found C, 71.01, H, 4.53, N, 11.21.

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