HETEROCYCLES, Vol. 68, No. 7, 2006, pp. 1409 - 1419. © The Japan Institute of Heterocyclic Chemistry
Received, 14th March, 2006, Accepted, 23rd May, 2006, Published online, 26th May, 2006. COM-06-10732

REGIO- AND *EXO*-π-FACIAL SELECTIVE 1,3-DIPOLAR CYCLOADDITION of α-(3-PYRIDYL)-*N*-PHENYLNITRONE TO NORBORNADIENE: ACTIVATION OF A π-BOND OF NORBORNADIENE AND CONTROL OF REGIO-CHEMISTRY OF NITRONE CYCLOADDITION BY NITRONE ADDITION TO THE OTHER DOUBLE BOND

Gurpinder Singh,[a] Munusamy Elango,[b] Venkatesan Subramanian,[b] and Mohan Paul Singh Ishar[a*]

[a]Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar 143 005, Punjab, India; Email mpsishar@yahoo.com
[b]Chemical Laboratory, Central Leather Research Institute, Adyar, Chennai 600 020, Tamilnadu, India

A*bstract*- Thermal cycloaddition of α-(3-pyridyl)-*N*-phenylnitrone to a π-bond in norbornadiene not only activates the other double bond towards 1,3-dipolar cycloaddition, it also regulates the regiochemistry of addition leading to regio- and *exo*-π-facial selective formation of novel 2:1 cycloadducts. A DFT analysis in terms of the global and local reactivity indices affords a rationalization of the obtained results.

INTRODUCTION

Cognizant of the well established 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 and theoretical[3] investigations of 1,3-dipolar cycloadditions, involving variedly substituted nitrones. Traditionally, the reactivity and selectivities in cycloaddition processes, including 1,3-dipolar cycloadditions, have been rationalized by frontier molecular orbital (FMO) approach,[4] however, recently applications of density functional theory (DFT)[3e,5] methods have provided an alternative reliable paradigm for understanding reactivity and selectivities in these processes. Particularly, the introduction of global electrophilicity index (ω) by Parr *et al.*[6] as a useful descriptor of

reactivity that allows a quantitative classification of global electrophilic character of a molecule and its extension to obtain local/regional electrophilicity indices has provided quantitative understanding of reactivity and regioselectivity in cycloadditions.[6] As a part of our continuing interest in the nitrone chemistry,[7] we have presently investigated the 1,3-dipolar cycloadditions of α-(3-pyridyl)-*N*-phenylnitrone[8] (**1**) with norbornadiene. The investigations were taken up because cycloadditions of the nitrone (**1**) with norbornadiene were to furnish novel polycyclic isoxazolidine analogs of nicotine (**2**) and epibatidine (**3**). Design and development of newer ligands for nicotinic-acetylcholine-receptors (nAChRs) is drawing considerable attention due to their potential applications in treatment of a variety of conditions[9] including Alzheimer's disease, as cognition enhancers[9c,e-g] and for the treatment of addiction to smoking.[9h] After isolation of epibatidine[10] (**3**), having useful non-opiod antinociceptive activity, there is increasing interest in the synthesis of related bicyclic-bridged system possessing useful pharmacological properties.[10,11] Though, a variety of heterocyclic systems have been reported to possess affinity for nicotinic receptors, there are very few examples where *N*-methylpyrrolidine moiety of nicotine has been replaced with other heterocyclic systems. Very recently isoxazolylmethylidene-quinuclidines (**4**) have been synthesized and shown to possess broad range of affinities for nicotinic and central muscarinc receptors.[12] Molecular modeling (MOPAC) of nicotine (**2**) and corresponding isoxazolidine analogs revealed that isoxazolidine moiety has nearly identical stereochemical features with a similar disposition of pyridyl moiety. However, the isoxazolidine analogues shall possess additional spatial (steric) and binding (electronic) components, and are, anticipated to possess useful pharmacological properties.

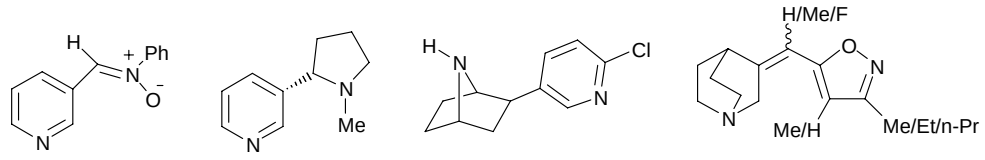


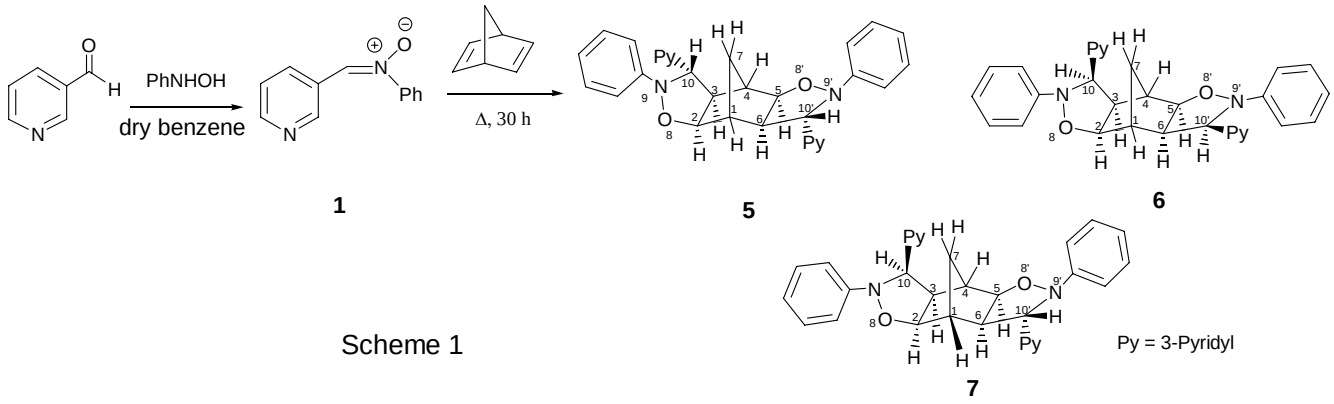
Fig. 1

Though addition of nitrones to norbornadiene has been examined, and the formation of 2:1 adducts in the reactions of *C*-phenyl-*N*-methyl/phenylnitrones with norbornadiene has been reported, however, no discussion of the observed regio-chemical outcome has been recorded.[13]

RESULTS AND DISCUSSION

Initially, reaction of nitrone[8c] (**1**), obtained by treating 3-formypyridine with *N*-phenylhydroxylamine, with norbornadiene (1.0 molar equivalent) was carried out by refluxing their dry-toluene solution for 30 h. Resolution of the complex mixture by column chromatography afforded a 1:2 cycloadduct (**5**, 12 %) as a pure component along with unreacted norbornadiene, and many other mixture fractions. Monitoring of the

various other fractions revealed that 2:1 adducts were the predominant components; these 2:1 addition products could be easily identified through the absence of olefinic proton resonances anticipated in the ^{1}H NMR spectra for possible 1:1 adducts. Subsequently, reaction of norbornadiene was carried out with two molar equivalents of nitrone (**1**) under similar conditions, when column chromatographic resolutions afforded adduct (**5**, 25 %) along with two more 2:1 cycloadducts (**6**, 32 %) and (**7**, 24 %) (Scheme 1). The assigned structures are based on detailed spectroscopic analysis, particularly, the NMR spectral data and comparison of the data with that of related norbornane derivatives and isoxazolidines[7c, d,14,15]; that these compounds are 2:1 cycloadducts of nitrone (**1**) with norbornadiene was corroborated by their mass spectral (ESI) and microanalytical data.



Scheme 1

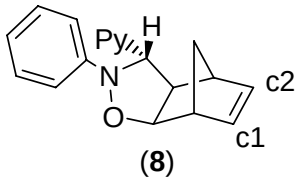
The easy characterization and beauty of compounds (**5**) and (**6**) lies in their highly symmetrical structure. In the ^{1}H NMR spectrum these compounds displayed, besides protons of the pyridine and phenyl moieties, only five resonances in the upfield part of their ^{1}H and ^{13}C NMR spectra. For instance, ^{1}H NMR spectrum of **5** displayed a doublet at δ 4.27(2 H, J = 6.5 Hz), which is attributed to C10-H & C10′-H and another doublet at δ 3.90 (2H, J = 6.6 Hz) is assigned to C2-H and C5-H. C1-H and C4-H appeared as a broad singlet (2H) at δ 2.67. The lack of any observable vicinal coupling of C1-H with C2-H or C6-H, and of C4-H with C3-H or C5-H was indicative of the *endo*-orientation[14] of C2-H, C6-H, C3-H, C5-H, or of *exo*-mode of addition of dipole as far as bicyclic norbornadiene system is concerned. In the case of **5,** C3-H and C6-H were present as an apparent triplet (2H, J ~ 6.7 Hz) at δ 2.39. C7-Hs in the case of **5,** were located as a 2H broad resonance at δ 2.06 and the downfield shifted position of C7-Hs as compared to the reported[14] chemical shift values for C7-Hs in a number of norbornane derivatives, was quite informative. Molecular modeling (MOPAC) revealed that in the energy minimized structure of **5**, the *N*-phenyl groups in the lowest energy invertomer are pushed upward, away from the pyridyl moieties, and are also tilted in a way so as to anisotropically deshield the C7-Hs. In the case of the stable invertomer of **6**, wherein the *N*-phenyl moieties are pushed downward, the C7-Hs resonance appeared at δ 1.28. The influence of these stereochemical changes is also reflected in the ^{13}C NMR spectra. In the case of **6**, the *N*-phenyl ring

is better oriented for resonance interaction with lone pair of nitrogen, consequently, in its ^{13}C NMR spectrum the *ortho*-carbons of *N*-phenyl moiety appear at δ 115.07 as compared to δ 118.70 in case of **5**. The stereochemistry at C10 and C10′ is based on $J_{3,10}$ and $J_{6,10'}$ - a low value of 6.5 Hz in case of **5** as compared to 9.2 Hz in case of **6** alludes to a *trans*- relationship between C3-H – C10-H, and C6-H – C10′-H in case of **5**, and *cis*-relationship in case of **6**; these conclusions are based on the premise that *cis*-vicinal coupling are always higher than *trans*-vicinal couplings in the case of isoxazolidines and related five membered-heterocycles.[7c,d] Structure of the third 2:1 adduct (**7**) has been similarly assigned by detailed spectroscopic analysis. The stereochemistry as *cis* around C3-C10 and as *trans* around C6-C10′ is again based on respective vicinal coupling constants $J_{3,10}$ = 9.2 Hz and $J_{6,10'}$ = 6.5 Hz; herein the C7-Hs appeared as an AB - quartet with δA 1.60 and δB 1.46 with $J_{A,B}$ = 15.4 Hz.

Mechanistically, the adduct (**5**) may be derived from addition of nitrone in its *E*-form to the *exo*-face of the norbornadiene π-bonds and compound (**6**) on the other hand is derived from addition of the *Z* (major) from of the nitrone to both π-bonds, whereas, **7** is derived from addition of one nitrone molecule in *Z*-form and other in *E*-form. Such equilibration of *Z* and *E* forms of nitrone and addition of minor isomer (*E*) is well known,[7c,d,16] and in the present case it is probably dictated by the steric constraints. Alternatively, it may be that only the *Z*-form of nitrone is involved and different stereochemical outcomes result from *endo*-/*exo*-modes of nitrone addition to the *exo*-π face of the norbornadiene-π-bonds. The involvement of both *E* and *Z* forms of the nitrone, or *exo*-/*endo*-additions of nitrone in its *Z*-form, is corroborated by the fact that on refluxing the isolated pure products for prolonged periods (> 10 h) only some deterioration occurred and no inter-conversion of adducts was observed as monitored by ^{1}H NMR, therefore, there is no isomerization of the adducts after initial addition. However, the important aspects of the present investigations, which deserved special attention were the enhancement of the reactivity of the remaining π-bond of norbornadiene after addition of one molecule of nitrone i.e., the preferred formation of 2:1 cycloadducts even when the reaction is carried out employing one molar equivalent of addends, the complete control of the regiochemistry of the second nitrone addition and complete *exo*-π-facial selectivity of additions.

For rationalizing these observations a recourse was made to DFT analysis because of the recent resounding success of this approach in rationalizing the outcome of cycloaddition processes, including 1,3-dipolar cycloadditions.[3d,e,17] According to DFT formalism addends in a cycloaddition process can be identified as nucleophilic or electrophilic components depending on their global electrophilic index (ω) value, leading to classification of the cycloaddition reactions as *normal* or *inverse-electron-demand* as has been done by FMO approach. According to this approach, the mechanism of cycloadditions changes

progressively from concerted synchronous to polar asynchronous process and ultimately to polar stepwise as $\Delta\omega$ (= ω_A - ω_B; ω_A & ω_B are electrophilic indices of addends A and B) increases.[3d,e,17,18] The regioselectivity is predicted by this approach in terms of regioisomeric pathways corresponding to the bond-formation between electrophilic and nucleophilic (less electrophilic) sites of the unsymmetrical reagents. The site with maximum f_k^+ is treated as site amenable to nucleophilic attack, whereas the one with maximum f_k^- is considered as site amenable to electrophilic attack[3d,e, 17,18]; the Fukui functions,[5] fk^+ and f_k^-, are thus calculated and utilized to predict the regioselectivites in case of cycloaddition processes. The results of DFT calculations[19] on nitrone, norbornadiene, norbornene and a possible 1:1 adduct (**8**) are incorporated in Table 1.



(**8**)

Table 1. Energy of the highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), chemical hardness (η), chemical potential (μ), static global elctrophilicity (ω) and static local indexes (f_k^+, f_k^-) values calculated at B3LYP/ 6-31G* level

Molecule	ω	E_{HOMO} (Hartrees)	E_{LUMO} (Hartrees)	η (eV)	μ (eV)	Site	f_k^+	f_k^-
Nitrone (**1**) *Z*	3.82	-0.2116	-0.0701	1.92	-3.83	N	0.059	0.046
						O	**0.095**	*0.184*
						C	0.083	0.106
Nitrone (**1**) *E*	3.65	-0.2088	-0.0669	1.93	-3.75	--	--	--
Norbornadiene	1.47	-0.2170	0.0002	2.95	-2.95	[a]C-olefinic	0.119	0.132
Norbornene	1.12	-0.2309	0.0256	3.49	-2.79	[b]C-olefinic	0.200	0.195
1:1 adduct (**8**)	1.85	-0.1898	-0.0233	2.27	-2.9	[c] C1	*0.023*	0.016
						[c] C2	0.016	**0.019**

a : All olefinic carbons in norbornadiene are equivalent
b: Both olefinic carbons in norbornene are equivalent.
c: C1 and C2 are indicated in structure (**8**).

The results indicate, that global electrophilic index (ω) value is higher for nitrone as compared to dipolarophiles, including **8**, indicating that nitrone is the electrophilic component and mono-adduct (**8**) shall be the nucleophilic component. It follows that the more reactive site in **8**, which is to act as nucleophile, is the atom C2 (highest f_k^- value) and the most reactive site in nitrone, as an electrophile, is the atom O (highest f_k^+ value). It may be noted that a reversal i.e., treating nitrone as nucleophile and **8** as electrophile would have reversed the regiochemistry of addition. It may be mentioned here that a

consideration of the opposite molecular dipolar alignments of the addends during addition also leads to the observed regioselectivity. The higher reactivity of **8** is also supported by higher value of ω as well as by other static parameters. Though, ω incorporates both μ and η, the former gives information about the flow of electrons where as relative reactivity is reflected in global chemical hardness (η). The data in Table-1 indicates that the possible 1:1 adduct (**8**) has lowest value of η among various dipolarophiles, signifying its lowest hardness or higher softness, hence higher nucleophilicity or reactivity. Interestingly, the adduct (**8**) also has a raised HOMO for the π-bond. The polarized and weakened nature of the remaining double bond in adduct (**8**) is also reflected in its increased length, which come to be 0.005 Å at B3LYP/6-31 G* level, and decreased bond order; as per calculations after addition of one nitrone molecule the bond order in the remaining olefinic bond is reduced from 1.9332 to 1.9151.[20]

Exo-π-facial selectivity in case of addition of phenyl azide to bicyclic olefins having bicyclo[2.2.1]-skeleton had led to enunciation of '*exo rule*' by Alder and Stein.[21] However, subsequent investigations had led to the observance of the violation of this rule.[13b,c] During present investigation formation of any *endo*-adduct has been ruled out by careful NMR scanning of various column fractions. Therefore, to rationalize the complete e*xo*-π-facial selectivity, energies of the various transitions states for addition to *exo*-π-face of norbornadiene and possible 1:1 adducts (**8**) leading to adducts (**5**) - (**7**), as well as corresponding additions to *endo*-π-face were calculated (Table-2).[22] The results reveal that all *exo*-facial-transition states lie substantially below the *endo*-facial-transition states, in consonance with the observed *exo*-*π*-facial selectivity. For above conclusion regarding lower energy of transition states for the observed modes of addition vis-à-vis the alternative regiochemistry and the π-facial selectivity geometries of all-plausible transitions state were optimized and energies were calculated at AM1 level, and compared.

Table 2. Relative energies of transition states for *Exo*- and *Endo*-π-facial addition of nitrone (**1**) to norbornadiene and a possible 1:1 adduct (**8**)

Sr. No.	*Exo*-π-facial T. States (Relative energies.)	*Endo*-π-facial T. States (Relative energies)	Relative stability of *exo*-π-facial T. States over *endo*-π-facial T. States (K. cal.)
1	A (0.2918922)	A' (0.3043281)	7.8
2	B (0.3793704)	B' (0.3847864)	3.4
3	C (0.3745989)	C' (0.3888009)	8.9
4	D (0.3738406)	D' (0.3896186)	9.9

Application of DFT theory thus provides a valuable rationalization of the complete control of

regiochemistry of second nitrone addition in such bicyclic systems. The theoretical calculation have also provided a rationalization for the observed *exo*-π-facial selectivity in accordance with the Alder - Stein "*exo rule*" for addition to such bicyclic systems. The lack of interconversions of isolated adducts on refluxing under the reaction conditions confirmed that the adducts are derived either from isomerization of nitrone under the reaction conditions and addition of both *E*- and *Z*-forms of nitrone or *endo*-/*exo*-modes of addition of the more stable *Z*-form of nitrone. Besides, the investigation have afforded novel polycyclic systems, including fascinating highly symmetrical (C_2 symmetric) molecules (**5**, **6**), which are anticipated to display interesting pharmacological properties

EXPERIMENTAL

General Information

Bruker AC-200FT (200 MHz) and JEOL AL-300FT (300 MHz) spectrometers were used to record ^{1}H NMR and ^{13}C NMR (50 & 75 MHz) spectra. Chemical shifts (δ) are reported as downfield displacements from TMS used as internal standard and coupling constants (*J*) are reported in Hz. IR spectra were recorded with Shimadzu DR-2001 FT-IR spectrophotometer on KBr pellets. Mass spectra, EI and ESI-methods, were recorded on Shimadzu GCMS-QP-2000A and Bruker Daltonics Esquire 300 mass spectrometers, respectively. Elemental Analyses were 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 Veego (make) MP-D digital melting point apparatus. All the calculations were performed using Gaussian 98 package. The molecules have been optimized at B3LYP/6-31G* level. All of them were found to be minimum on the potential energy surface with zero imaginary frequency. Global reactivity indexes were calculated using the working equations available in the literature. Local reactivity indices, Fukui functions, have been calculated using the DMOL program implemented in Cerius 2 package employing Hershfeld populations scheme.

Reaction of 1.0 molar equivalent of nitrone (1) with norbornadiene

To a solution of nitrone[8c] (**1**, 300 mg) in dry toluene (60 mL) was added norbornadiene (140 mg, 1.0 molar equiv.) and the solution was refluxed with stirring. After the completion of reaction, (30 h, TLC) the solvent was removed under reduced pressure. Column chromatographic resolution (SiO_2 60-120 mesh, 20 g, column packed in hexane, hexane: AcOEt gradient as eluent) of the product mixture afforded adduct (**5**, hexane - AcOEt, 7:3) as a light yellow solid (90 mg), mp 189-191°C (ether). IR 1259, 1317, 1471, 1489, 1542, 1595, 2924, 3057 cm^{-1}; ^{1}H NMR δ 2.06(br d, 1H, *J* = 2.8 Hz, C7-Hs), 2.39(unresolved dd, 2H, *J* ~ 6.7 Hz, C3-H & C6-H), 2.67(bs, 2H, C1-H & C4-H), 3.90(d, 2H, *J* = 6.6 Hz, C2-H & C5-H), 4.27(d, 2H, *J* = 6.5 Hz, C10-H & C10′-H), 6.80(d, 4H, *J* = 7.5 Hz, arom-Hs), 7.00(t, 2H, *J* = 7.1 Hz, arom-Hs),

7.17 (unresolved dd, 4H, *J* ~ 7.5 Hz, arom.-Hs), 7.34(td, 2H, *J* = 6.9 Hz & 4.8 Hz, 2 × C5-H of Py), 7.80(bd, 2H, *J* = 6.9 Hz, 2 × C4-H of Py), 8.65-8.58(m, 4H, 2 × C2-H and 2 × C6-H of Py); ^{13}C NMR δ 27.39, 42.26, 58.33, 71.90, 81.67, 118.70, 123.90, 124.05, 128.50, 134.60, 136.99, 148.72, 149.46, 148.75; MS (ESI) *m/z*: 489(M + H)$^+$. Anal. Calcd for $C_{31}H_{28}N_4O_2$: C, 76.21; H, 5.78; N, 11.47. Found C, 76.29; H, 5.83; N 11.39.

Reaction of 2.0 molar equivalents of nitrone (1) with norbornadiene

Norbornadiene (140 mg, 1.52 mmol) was added to a solution of nitrone (**1**, 600 mg, 2.0 molar equiv.) in dry toluene (100 mL) and the contents were refluxed with stirring. After the completion of reaction, (30h, TLC) the solvent was removed with traces removed under reduced pressure. Column chromatographic (SiO_2 60-120 mesh, 20g, column packed in hexane, hexane: AcOEt gradient eluent) resolution of the product mixture afforded adduct (**6**, 225 mg, hexane: AcOEt 9:1) as light yellow solid, mp 110-112°C (ether). IR 1217, 1255, 1287, 1312, 1352, 1421, 1452, 1488, 1574, 1595, 2942, 2988, 3030, cm^{-1}; ^{1}H NMR δ 1.30 (s, 2H, C7-Hs), 2.03(s, 2H, C1-H & C4-H), 2.70(dd, 2H, *J* = 9.2 and 6.5 Hz, C3-H & C6-H), 4.30(d, 2H, *J* = 6.5 Hz, C2-H & C5-H), 4.96(d, 2H, *J* = 9.2 Hz, C10-H & C10′-H), 7.00-6.85(m, 6H, arom-Hs), 7.30-7.12(m, 6H, arom-Hs and 2 × C5-H of Py), 7.76(d, 2H, *J* = 7.8 Hz, 2 X C4-H of Py), 8.54(dd, 1H, *J* = 6.26 and 4.38 Hz, 2 × C6-H of Py), 8.63(s, 2H, 2 × C2-H of Py); ^{13}C NMR δ 28.30, 40.08, 52.66, 69.02, 84.42, 115.07, 122.35, 123.27, 128.94, 134.25, 135.10, 148.63, 148.84, 150.28, MS (ESI) *m/z*: 489(M + H)$^+$. Anal. Calcd for $C_{31}H_{28}N_4O_2$: C, 76.21; H, 5.78; N 11.47. Found C, 76.19; H, 5.73; N 11.35.

Further elution with hexane: ethyl acetate (8:2) afforded adduct (**7**) (170 mg) as yellow solid, mp 148-150°C (ether). IR 1217, 1234, 1260, 1320, 1341, 1371, 1431, 1444, 1461, 1478, 1491, 1542, 1564, 1581, 1602, 2983, 2938, 3042, cm^{-1}; ^{1}H NMR δ 1.64 -1.42 (AB quartet, δA = 1.60 & δB = 1.46, J_{AB} = 15.4 Hz, C7- Hs), 2.07(bs, 1H, C4-H), 2.39(unresolved dd, 1H, *J* ~ 6.7 Hz, C6-H), 2.63(br, 1H, C1-H), 2.69(dd, 1H, *J* = 9.2 and 6.9 Hz C3-H), 3.77(d, 1H, *J* = 6.9 Hz, C2-H), 4.24(d, 1H, *J* = 6.5 Hz, C10′-H), 4.32(d, 1H, *J* = 6.4 Hz, C5-H), 5.05(d, 1H, *J* = 9.2 Hz, C10-H), 7.00-6.80(m, 6H, arom.-Hs), 7.37-7.08(m, 6H, arom-Hs and 2 × C5-H of Py), 7.76(d, 1H, *J* = 7.8 Hz, C4-H of Py), 7.86(d, 1H, *J* = 7.1 Hz, C4-H of Py), 8.58(d, 2H, *J* = 4.9 Hz, 2 × C6-H of Py), 8.71 (broad, 2H, 2 × C2-H of Py); ^{13}C NMR δ 27.76, 41.63, 41.06, 51.81, 59.06, 69.16, 71.80, 82.21, 84.40, 114.97, 118.83, 122.34, 124.01, 123.23, 124.24, 128.56, 128.97, 134.86, 134.29, 135.90, 135.80, 148.12, 148.67, 150.26, 149.50, 148.97, 148.79; MS (ESI) *m/z*: 489(M + H)$^+$. Anal. Calcd for $C_{31}H_{28}N_4O_2$:C, 76.21; H, 5.78; N 11.47. Found C, 76.15; H, 5.70; N, 11.33.

Further elution with hexane – AcOEt (7:3) afforded adduct (**5**) (178 mg).

ACKNOWLEDGEMENTS

Use of 300 MHz NMR facilities provided by the Department of Science and Technology, Government of India, at Chemistry Department, Guru Nanak Dev University, Amritsar, is gratefully acknowledged.

REFERENCES AND NOTES

1. (a) W. R. Carruthers, 'Cycloadditions in Organic Synthesis,' Pergamon Press, London, 1990, Chapter 6, p 269. (b) J. J. Tuffariello, 'Nitrones in 1,3-Dipolar Cycloaddition Chemistry,' Vol. 2, ed. by A. Padwa, Wiley Interscience, New York, 1984. (c) L. A. Paquette, 'Comprehensive Organic Synthesis,' Vol. 5, ed. by B. M. Trost, and I. Fleming, Pergamon, Oxford, 1991, Chapter 3. (d) M. Frederickson, *Tetrahedron* 1997, **53**, 403. (e) K. V. Gothelf and K. A. Jorgenson, *Chem. Rev.*, 1998, **98**, 863. (f) A. Padwa and A. M. Schoffstall, 'Advances in Cycloaddition,' ed. by D. P. Curran, JAI Press, Greenwich. 1990, p 2. (g) S. E. Denmark and A. Thorarensen, *Chem. Rev.*, 1996, **96**, 137. (h) K. V. Gothelf and K. A. Jorgensen, 'Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry towards Heterocycles and Natural Products,' Vol. 59, ed. by A. Padwa and W. Pearson, Wiley-VCH, Weinheim, 2002, p 864.
2. (a) K. B. Simonsen, P. Bayon, R. G. Hazell, K. V. Goethelf, and K. A. Jorgensen, *J. Am. Chem. Soc.*, 1999, **121**, 3845. (b) O. Tamura, K. Gotanda, J. Yoshino, Y. Morita, R. Terashima, M. Kikuchi, T. Miyawaki, N. Mita, M. Yamashita, H. Ishibashi, and M. Sakamoto, *J. Org. Chem.*, 2000, **65**, 8544. (c) H. G. Aurich, M. Geiger, C. Gentes, K. Harms, and H. Koster, *Tetrahedron*, 1998, **54**, 3181. (d) U. Chiacchio, A. Cosaro, D. Innazo, A. Piperno, A. Procopio, A. Rescifena, G. Romeo, and R. Romeo, *J. Org. Chem.*, 2002, **67**, 4380. (e) A. Long and S. W. Baldwin, *Tetrahedron Lett.*, 2001, **42**, 5343. (f) P. Merino, S. Anoro, S. Franco, F. L. Merchan, T. Tejero, and V. Tunon, *J. Org. Chem.*, 2000, **65**, 1590. (g) C. Dagoneau, A. Tomassini, J.-N. Denis, and Y. Valle, *Synthesis*, 2001, 150. (h) A. Broggini, C. La Rosa, T. Rilati, A. Terraneo, and G. Zeechi, *Tetrahedron*, 2001, **57**, 8323. (i) F. Djapa, K. Ciamala, J.-M. Melot, J. Vebrel, and G. Herlem, *J. Chem. Soc., Perkin Trans. I*, 2002, 687.
3. (a) C. D. Valentin, M. Freccro, R. Gandolfi, and A. Rastelli, *J. Org. Chem.*, 2000, **65**, 6112. (b) M. A. Silva, and J. M. Goodman, *Tetrahedron*, 2002, **58**, 3667. (c) P. Merino, J. Revuelta, T. Tejero, U. Chiacchio, A. Rescifina, and G. Romeo, *Tetrahedron*, 2003, **59**, 3581 and references cited therein. (d) P. Perez, L. R. Domingo, M. J. Aurell, and R. Contreras, *Tetrahedron*, 2003, **59**, 3117 and references cited therein. (e) L. Domingo, *Eur. J. Org. Chem.*, 2000, 2265. (f) R. Herrera, A. Nagarajan, M. A. Morales, F. Mendez, H. A. Jimenez-Vazquez, L. G. Zepeda, and J. Tamariz, *J. Org. Chem.*, 2001, **66**, 1252.
4. (a) K. Fukui, *Acc. Chem. Res.*, 1981, **14**, 363. (b) K. Fukui, *Acc. Chem. Res.*, 1971, **4**, 57. (c) I. Fleming, 'Frontier Orbitals and Organic Chemical Reactions,' Wiley-Chichester, 1976. (d) K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *J. Am. Chem. Soc.*, 1973, **95**, 7301. (e) K. N. Houk, J.

Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.*, 1973, **95**, 7287.

5. (a) R. G. Parr and W. Yang, 'Density Functional Theory of Atoms and Molecules,' Oxford University Press, New York, 1989. (b) P. Geerling, F. De Proft, and W. Langenaeker, *Chem. Rev.*, 2003, **103**, 1973.
6. R. G. Parr, L. V. Szentpaly, and S. Liu, *J. Am. Chem. Soc.*, 1999, **121**, 1922. (b) H. Chermette, *J. Comp. Chem.*, 1999, **20**, 129. (c) The global electrophilicity descriptor ω measures the stabilization energy when the system acquires the additional electronic charge ΔN from the environment.
7. (a) M. P. S. Ishar, K. Kumar, and R. Singh, *Tetrahedron Lett.*, 1998, **39**, 6547. (b) M. P. S. Ishar and K. Kumar, *Tetrahedron Lett.*, 1999, **40**, 175. (c) N. K. Girdhar and M. P. S. Ishar, *Tetrahedron Lett.*, 2000, **39**, 7551. (d) M. P. S. Ishar, G. Singh, K. Kumar, and R. Singh, *Tetrahedron*, 2000, **56**, 7817.
8. (a) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, 1967, 4179. (b) M. Miura, M. Enna, K. Okuro, and M. Nomura, *J. Org. Chem.*, 1995, **60**, 4999. (c) G. Singh, M. P. S. Ishar, N. K. Girdhar, and L. Singh, *J. Heterocycl. Chemistry***,** 2005, **42**, 1047.
9. (a) M. W. Holladay, M. J. Dart, and J. K. Lynch, *J. Med. Chem.*, 1997, **40**, 4169 and references cited therein. (b) J. R. Lennox, S. C. Turner, and H. Rapoport, *J. Org. Chem.*, 2001, **66**, 7078. (c) J. D. Schmitt and M. Bencherif, *Ann. Rep. Med. Chem.*, 2000, **35**, 41. (d) T. Ullrich, D. Binder, and M. Myerin, *Tetrahedron Lett.*, 2002, **43**, 177. (e) B. Badio, D. Shi, M. Garraffo, and J. W. Daly, *Drug Dev. Research*, 1995, **36**, 46. (f) M. W. Decker and M. D. Meyer, *Biochem. Pharmacol.*, 1999, **58**, 917. (g) J. P. Sullivan and A. W. Bannon, *Drug Rev.*, 1996, **2**, 21. (h) F. I. Carrol, J. R. Lee, H. A. Navarro, L. E. Brieaddy, P. Abraham, M. I. Damaj, and B. R. Martin, *J. Med. Chem.*, 2001, **44**, 4039.
10. T. F. Spande, H. M. Garaffo, M. W. Edwards, H. J. C. Yeh, L. Pannell, and J. W. Daly, *J. Am. Chem. Soc.*, 1992, **14**, 3475.
11. (a) F. I. Carroll, F. Liang, H. A. Navarrco, L. E. Brieaddy, P. Abraham, M. I. Damaz, and B. R. Martin, *J. Med. Chem.*, 2001, **44**, 2229. (b) C. Hedberg, P. Pinho, P. Roth, and P. G. Andersson, *J. Org. Chem.*, 2000, **65**, 2810. (c) D. M. Hodgson, C. R. Maxwell, R. Wisedale, I. R. Matthews, K. J. Carpenter, A. H. Dickenson, and S. Wonnacott, *J. Chem. Soc., Perkin Trans. I*, 2001, 3150. (d) D. Che, T. Wegge, M. T. Stubbs, G. Seitz, H. Meier, and H. Methfessel, *J. Med. Chem.*, 2001, **44**, 47. (e) C. G. V. Sharples, G. Karig, G. L. Simpson, J. A. Spencer, E. Wright, N. S. Millar, S. Wonnacott, and T. Gallagher, *J. Med. Chem.*, 2002, **45**, 3235. (f) J. P. J. Seerden, M. Th., M. Tulp, H. W. Scheeren, and C. G. Kruse, *Biorg. Med. Chem.*, 1998, **6**, 2103. (g) A. Sutherland, T. Gallagher, C. G. V. Sharples, and S. Wonnacott, *J. Org. Chem.*, 2003, **68**, 2475. (h) Z. Liang, Y. Xiao, C. George, K. J. Kellar, and A. P. Kozikowski, *Org. Biomol. Chem.*, 2003, **1**, 3878. (j) Z.-L. Wei, P. A. Petukhov, Y. Xiao, W. Tuckmantel, C. George, K. J. Kellar, and A. P. Kozikowski, *J. Med. Chem.*, 2003, **46**, 921.
12. J. E. Tender, J. B. Hansen, M. Begturp, I. Pettersson, K. Rimvall, B. Christensen, U. Ehrbar, and P. H.

Olesen, *J. Med. Chem.*, 1999, **42**, 4970.

13. (a) R. Huisgen, R. Garshey, H. Hauck, and H. Seidl, *Chem. Ber.*, 1968, **101**, 2043. (b) H. Taniguchi, T. Ikeda, Y. Yoshida, and E. Imoto, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 2694. (c) H. Taniguchi, T. Ikeda, Y. Yoshida, and E. Imoto, *Chem. Lett.*, 1976, 1139.
14. (a) L. M. Jackman and S. Sternhel, 'Applications of NMR Spectroscopy,' Pergamon, Oxford, 1969, pp 61-113 and 215-248. (b) R. P. Gandhi, M. P. S. Ishar, and A. Wali, *J. Chem. Soc., Chem. Commun.*, 1990, 1074. (c) E. W. G. Jun, *Chem. Comm.*, 1968, 332. (d) P. M. Subramaniam, M. T. Emerson, and N. A. Label, *J. Org. Chem.*, 1965, **30**, 2624. (e) E. I. Synder and B. Frenjus, *J. Am. Chem. Soc.*, 1964, **86**, 1166. (f) A. P. Marchand and J. E. Rose, *J. Am. Chem. Soc.*, 1968, **90**, 3724. (g) B. Franzus, W. C. Baird, N. F. Chamberlain, T. Hines and E. I. Snyder, *J. Am. Chem. Soc.*, 1968, **90**, 3721.
15. E. Lippmaa, T. Pehk, J. Paasivirta, N. Belikova, and A. Plate, *Org. Magn. Reson.*, 1970, **2**, 581.
16. (a) A. Padwa, L. Fisera, K. F. Koehler, A. Rodriguez, and G. S. K. Wong, *J. Org. Chem.*, 1984, 49, 276 and references cited therein. (b) L. W. Boyle, M. J. Peagram, and G. H. Whitham, *J. Chem. Soc. B*, 1971, 1728;,(c) J. Biorgo, D. R. Boyd, and D. C. Neil, *J. Chem. Soc., Chem. Commun.*, 1974, 478. (d) L. W. Boyle, M. J. Peagram, and G. H. Whitham, *J. Chem. Soc., Perkin Trans. 1*, 1977, 247.
17. (a) L. R. Domingo, M. J. Aurell, P. Perez, and R. Contreras, *Tetrahedron*, 2002, **58**, 4417. (b) L. R. Domingo, M. J. Aurell, P. Perez, and R. Contreras, *J. Org. Chem.*, 2003, **68**, 3884. (c) L. R. Domingo, M. J. Aurell, P. Perez, and R. Contreras, *J. Phys. Chem. A*, 2002, **106**, 6871.
18. (a) M. J. Aurell, L. R. Domingo, P. Perez, and R. Contreras, *Tetrahedron*, 2004, **60** 11503. (b) P. Perez, *J. Org. Chem.*, 2003, **68**, 5886.
19. DFT calculations were performed using Gaussian 98 package (M. J. Frisch, et. al., Gaussian 98, Revision A.5, Gaussian Inc., Pittsburg, PA, 1998). The equations used for calculating chemical hardness, chemical potential and elctrophilicity are: $\eta = (I-A)/(2)$; $\mu = -[(I+A)/(2)]$; $\omega = (\mu*\mu)/(2*\eta)$ where vertical ionization energy, $I = E_{HOMO}$ and vertical electron affinity, $A = E_{LUMO.}$
20. Bond order determined using Wiberg bond indices employing the nbo program (K. Wiberg, *Tetrahedron*, 1968, **24**, 1083).
21. (a) K. Alder and G. Stein, *Ann. Chem.*, 1931, **485**, 223 & 211. (b) K. Alder and G. Stein, *Ann. Chem.*, 1933, **501**, 1. (c) K. Alder and G. Stein, *Ann. Chem.*, 1935, **515**, 185. (d) K. Alder, H. J. Ache, and F. H. Flock, *Chem. Ber.*, 1960, **93**, 1888.
22. The transition states were located at AM1 level of theory and were found to possess one imaginary frequency.