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[3+2] Cycloadditions. Part XXXIII. Selective cycloadditions of *C*-(1-naphthyl)-*N*-methyl nitrone and *C*-phenyl-*N*-benzyl nitrone to α,β-unsaturated carbonyl compounds[1,2]

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[3+2] Cycloadditions [32CA] involving nitrones as 1,3-dipolar species to alkenes yield isoxazolidines, which on further transformations can be converted to naturally occurring bioactive compounds. Thus the 32CA route provides conversion of simple natural products to more complex natural occurring bioactive nitrogen heterocycles, and close analogues. The present work deals with 32CA between the nitrones *C*-(1-naphthyl)-*N*-methyl nitrone and *C*-phenyl-*N*-benzyl nitrone to α,β-unsaturated carbonyl compounds as dipolarophiles, *viz.* arylidene malonate esters, methyl cinnamate and benzylidene acetophenone (chalcone). Methyl cinnamate is a naturally occurring compound, while the chalcone scaffold is present in several natural products. Structure elucidation of the generated cycloadducts have been achieved by means of detailed spectroscopic and XRD studies. All the cycloadditions investigated occurr regioselectively to yield tetra/penta-substituted isoxazolidines, where the carbonyl group(s) are situated at the 4-position of the isoxazolidine ring. DFT computations including optimised geometries, FMO energies, electronic chemical potentials, chemical hardness, chemical softness and reactivity indices of a number of the reactants have been calculated at DFT/B3LYP/6-31++G(d,p) level of theory. The calculated reactivity indices have been used to analyse the 32CAs studied and to predict the regioselectivities; the predictions are in excellent accord with the experimental results.

Keywords: Nitrones, cycloadditions, isoxazolidines, XRD, DFT

[3+2] Cycloadditions of nitrones to olefins offer a versatile route to generate 5-membered heterocycles[3, 4]. The isoxazolidines formed can act as templates in the synthesis of various bioactive natural products[3]. Isoxazolidines allow considerable regiochemical and stereochemical control during cycloaddition, and can be functionalised. Hence it is of importance to design 32CA reactions of nitrones to olefinic substrates with high regio- and stereoselectivity. We have been carrying out systematic investigations on different aspects of the [3+2] cycloadditions of nitrones for the past several years[2, 4-7], with particular emphasis on the reactions of acyclic and cyclic nitrones to dipolarophiles containing a double bond conjugated with an electron-withdrawing group. We have carried out DFT computations to rationalise the reactivities and selectivities of [3+2] cycloaddition reactions in a number of communications[2a,4a,7].

Reactive species such as nitrones are traditionally referred to as 1,3-dipolar species. 1,3-Dipoles are 4π-electron systems, where the π-electrons are delocalised over three atomic centres with a central heteroatom (usually oxygen, nitrogen or sulphur) comprising an empty π-orbital along with two occupied π-orbitals. In valence bond terms, the electronic structures of 1,3-dipolar species are represented as resonance hybrids of charge-separated canonical forms with opposite charges in a 1,3-relationship; hence the 1,3-dipole nomenclature of these species. It should be noted, however, the dipolar species are polarised entities without total separation of positive and negative charges. Further, the polarisation of these species depend on the three atoms present in the functional group and depend on the substituents present. In recent years, these species are being increasingly referred to as 4π-Three Atom Components (TAC).

We have done extensive work with the *C*,*N*-diarylnitrones and *C*-aryl-*N*-methyl nitrones, where the aryl group was phenyl or substituted

phenyl[2,4-7]. The present communication is an extension of our earlier studies. It describes reactions of *C*-(1-naphthyl)-*N*-methyl nitrone (**1**) (where the *C*-phenyl/substituted phenyl ring is replaced by a *C*-1-naphthyl ring), and *C*-phenyl-*N*-benzyl nitrone (**9**) (where the *N*-methyl group is replaced by a *N*-benzyl group). On going through earlier literature, we could not find any report on *C*-(1-naphthyl)-*N*-methyl nitrone. The dipolarophiles selected for the present study were α,β-unsaturated carbonyl compounds, where an electron-withdrawing carbonyl group was conjugated with a double bond – arylidene malonate esters, methyl cinnamate and benzylidene acetophenone (chalcone). Methyl cinnamate is a naturally occurring compound, while the chalcone scaffold is present in several natural products. Thus the 32CA route to isoxazolidines provides conversion of simple natural products to more complex natural occurring bioactive nitrogen heterocycles and close analogues. Structure elucidations of the generated cycloadducts were achieved by means of detailed spectroscopic analysis and X-ray diffraction (XRD). The results are summarised in Scheme I and Scheme II.

Results and Discussions

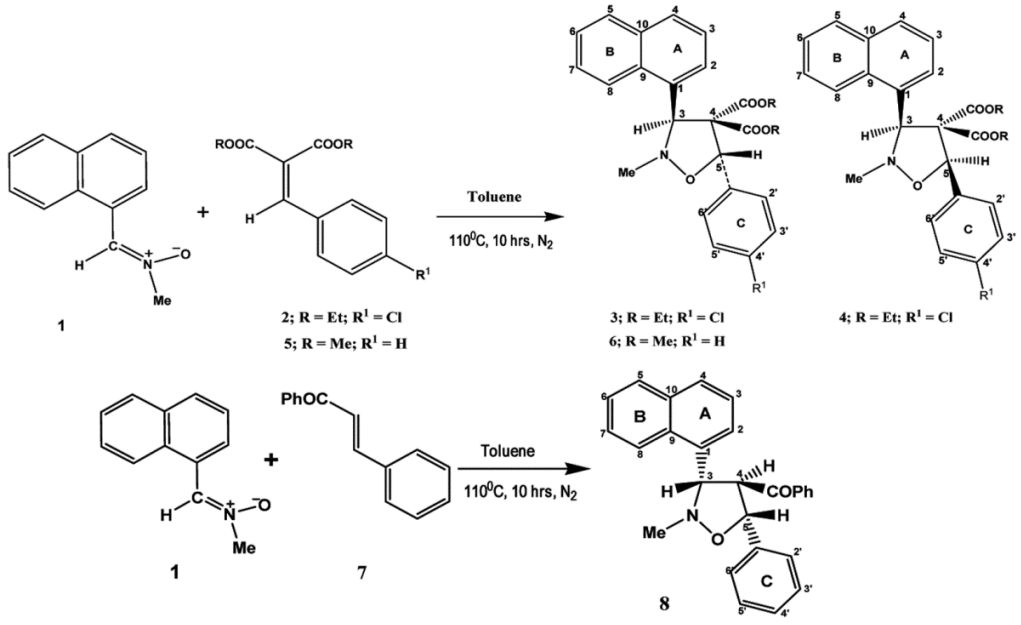
[3+2] Cycloadditions of *C*-(1-naphthyl)-*N*-methyl nitrone (1)

C-(1-naphthyl)-*N*-methyl nitrone (**1**), m.p. 94ºC, was prepared from 1-naphthaldehyde and *N*-methyl hydroxylamine hydrochloride by microwave assisted procedure developed earlier by us[8, 9], and fully characterized by spectroscopical studies.

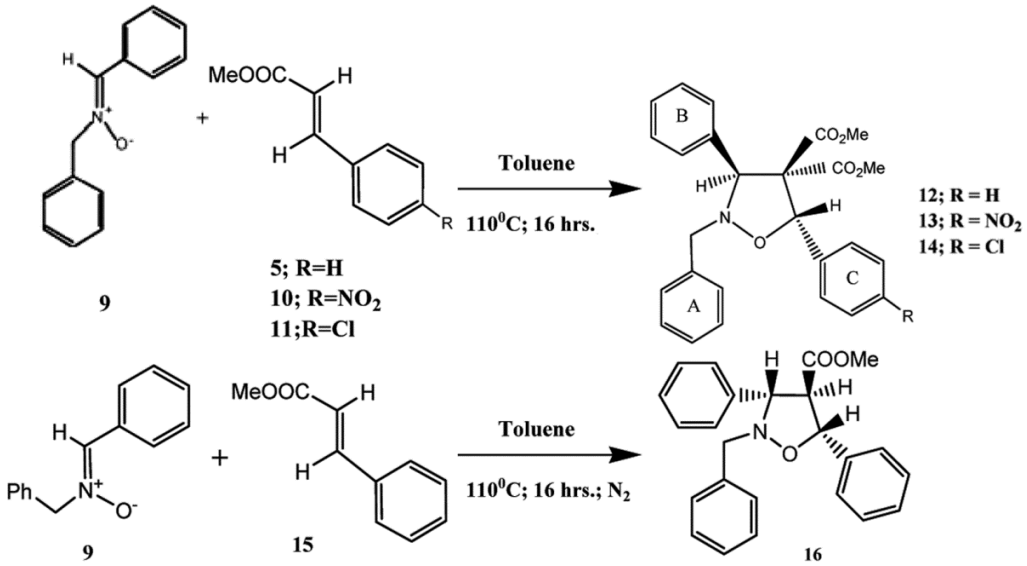
Three dipolarophiles, *viz.* (**2**), (**5**) and (**7**), were selected for 32CAs with *C*-(1-naphthyl)-*N*-methyl nitrone (**1**) (Scheme I).

The reactions were carried out in refluxing anhydrous toluene (~110°C) under nitrogen atmosphere for 10 hours with 1:3 molar ratio (dipole: dipolarophile) of the reactants. The reactions were monitored by TLC and 300 MHz ^{1}H-NMR analysis of aliquots removed from time to time. The reactions were worked up by removal of solvent under reduced pressure in a Büchi rotary evaporator (the crude post-reaction mixture was analysed by TLC and ^{1}H-NMR), followed by chromatography over neutral alumina.

Reaction of *C*-(1-naphthyl)-*N*-methyl nitrone (**1**) with a three-molar excess of diethyl 4-chlorobenzylidene malonate (**2**) was carried out in refluxing toluene for 10 hours. ^{1}H-NMR analysis of the crude product showed the presence of essentially only one product **3** (88% yield) together with small amounts of a minor product **4** (4%), with a total conversion of 92%. Product **3** was purified by chromatography over neutral alumina and was obtained in the hexane: ethyl acetate (4:1) eluates. **3** crystallised from hexane-$CHCl_3$ (1:1) as colorless crystals, m.p. 108ºC. The minor product **4** could not be isolated, being only detected in the crude reaction mixture by ^{1}H-NMR analysis.



Scheme I — [3+2] Cycloadditions of *C*-(1-naphthyl)-*N*-methyl nitrone **1**



Scheme II — [3+2] Cycloadditions of *C*-phenyl-*N*-benzyl nitrone **9**

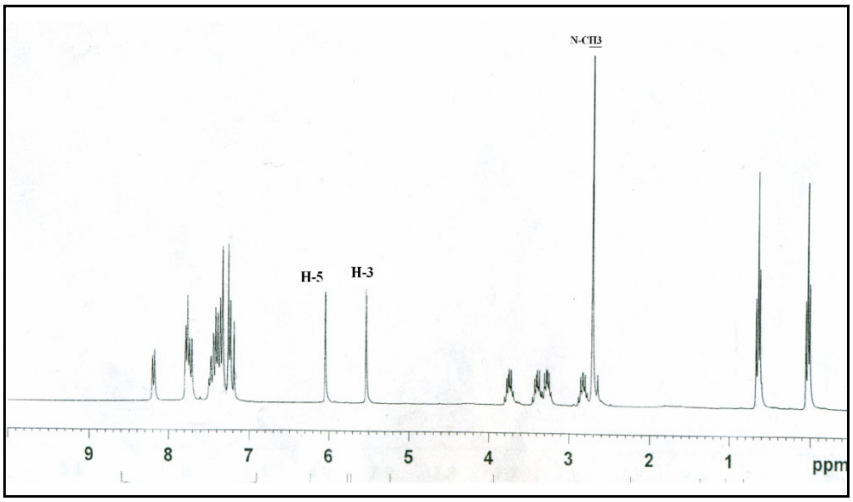


Figure 1 — 300 MHz ^{1}H NMR spectrum of 3 ($CDCl_3$)

Structure of cycloadduct 3,5-*trans*-2-methyl-3-(1-naphthyl)-5-(4'-chlorophenyl)-4,4-dicarbethoxy isoxazolidine (**3**) was elucidated by spectroscopic analysis and XRD studies. 300 MHz ^{1}H NMR spectrum (Figure 1) of **3** showed singlets at δ 5.54 (H-3) and δ 6.05 (H-5). Coupling inter-relationships of the proton signals were confirmed from the 300 MHz ^{1}H-^{1}H COSY (Figure 2) and LR-COSY spectra (complete assignments in Experimental). Cross peaks in the LR-COSY spectrum indicated long-range couplings of H-3 and H-5 with the *ortho*-protons of the attached aromatic rings A and C, thus confirming the regiochemistry of the product: H-3 (δ 5.54) and H-5 (δ 6.05) showed long range correlations respectively with H-2 of naphthyl ring A (δ 7.39) and with δ 7.33 (H-2 and H-6) of phenyl ring C. Ethyl proton assignments in the cycloadduct could be also differentiated from their respective correlations in the COSY spectrum. The 75.5 MHz ^{13}C NMR spectrum showed the isoxazolidine ring carbons at δ 73.48 (C-3), δ 74.88 (C-4), and δ 83.60 (C-5). NMR assignments were made by comparison with similar cycloadducts having isoxazolidine ring with 3,5-diaryl substituents[6].

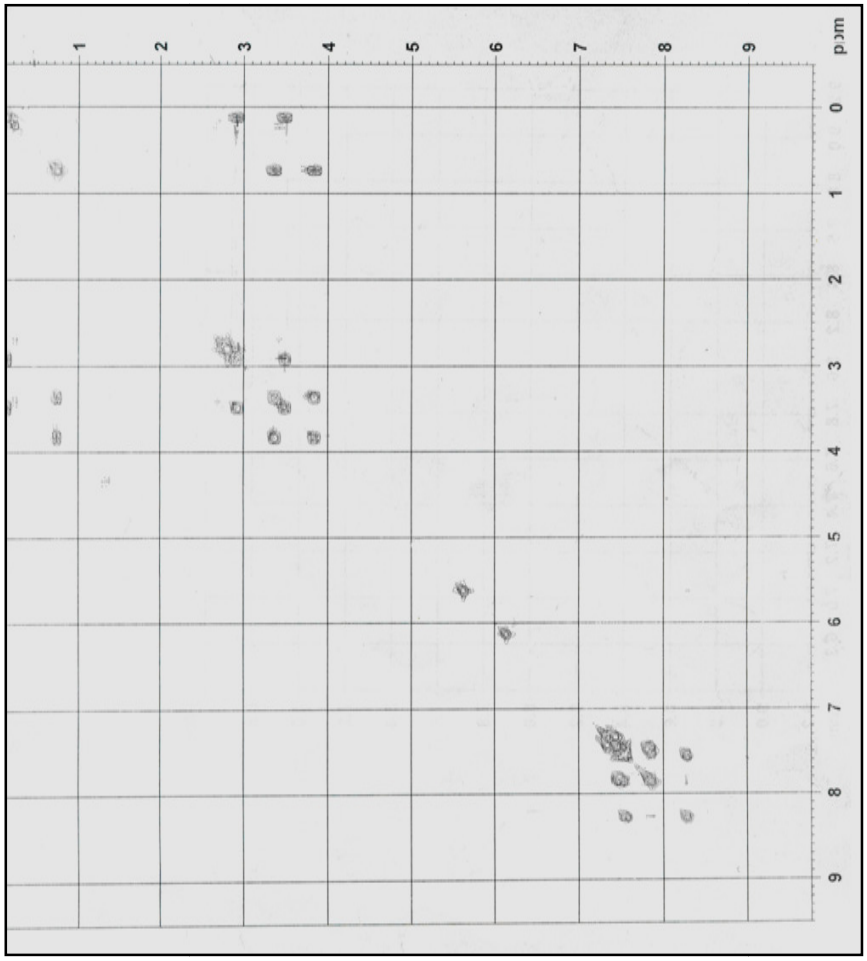


Figure 2 — 300 MHz ^{1}H-^{1}H COSY of 3 ($CDCl_3$)

The structure and relative stereochemistry of **3** was confirmed by single crystal XRD analysis. Cycloadduct **3** was recrystallised by slow evaporation from hexane-chloroform (1:1) to obtain single crystals. XRD studies were carried out with selected crystals mounted in cryo-loops and stored at 100ºK in liquid nitrogen. Diffraction data were recorded on a NONIUS KAPPA CCD diffractometer operating the Mo Kα radiation (λ = 0.7107 Å). Recordings were done under cryotemperature conditions at −50°C.The crystals are Triclinic, Space group P-1 (Z = 2), with cell parameters a, 7.691(1) Å; b, 12.639(1) Å; c, 13.260(1) Å; α, 114.80(5)^{0}; β, 99.30(4)°; γ, 91.76(5)° (see Experimental). The ORTEP view of a single molecule is shown in Figure 3. This confirmed the relative stereochemistry of **3** as having a 3,5-*trans* orientation. The N2 lone pair is inverted and is *trans* with respect to H-3. The five-membered ring is more or less in the envelope conformation with C5 out of the plane. It is

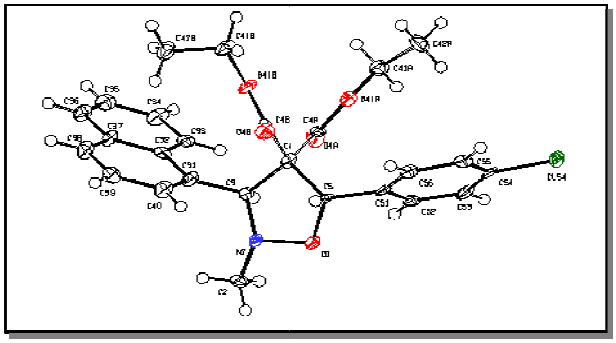


Figure 3 — Structure and stereochemistry of cycloadduct 3 derived from single crystal XRD studies

interesting to note that the methyl group of the 4-β-carbethoxy group falls right over the naphthyl ring. This is reflected in the upfield shift of this methyl signal, and aided the assignments. The numberings of structures as given in these projections are those provided in the X-ray crystallographic analysis outputs.

^{01}H NMR analysis of the crude product indicated a minor product **4** (4%). Since the H-3 and H-5 (δ 5.03 and δ 6.27) NMR signals of the minor product were singlets like those of the major product, it was confirmed this would be the diastereoisomeric 3,5-*cis* isomer (**4**). It is to be noted that the signals of H-3 and H-5 appear at a comparatively greater difference from each other in **4** compared to **3**.

Reaction of *C*-(1-naphthyl)-*N*-methyl nitrone (**1**) with a three-molar excess of dimethyl benzylidene malonate (**5**) was carried out in refluxing toluene for 10 hours. 300 MHz ^{1}H NMR analysis of the crude product showed the presence of only one product **6,** $C_{24}H_{23}NO_5$. Chromatography over neutral alumina and recrystallisation from hexane-chloroform (1:1) gave colourless crystals, m.p.102ºC. Its IR (KBr) spectrum showed bands at 1727 cm^{-1}(unconjugated carbonyl); 852, 811, 751, 692 cm^{-1} (aromatic rings). 300 MHz ^{1}H NMR spectrum ($CDCl_3$) of adduct **6** showed singlets at δ 4.64 (H-3) and δ 5.95 (H-5). The isoxazolidine ring carbons appeared at δ 77.87 (C-3), δ 75.34 (C-4), and δ 84.03 (C-5). The two quaternary carbonyl carbons appeared at δ 168.43 and δ 168.22. From a comparison of chemical shifts of similar cycloadducts to dialkyl malonates obtained in earlier investigations[6] and 3, it was apparent that the product is 3,5-*trans*-2-methyl-3(1-naphthyl)-5-phenyl-4,4-dicarbmethoxy isoxazolidine (**6**) with the H-3 and H-5 *trans* to each other.

Reaction of *C*-(1-naphthyl)-*N*-methyl nitrone (**1**) with a three-molar excess of benzylidene acetophenone (**7**) yielded a single cycloadduct **8**, $C_{27}H_{23}NO_2$, m.p. 94ºC. Its IR (KBr) spectrum showed a band at 1659 cm^{-1} for conjugated ketone carbonyl group. The 300 MHz ^{1}H NMR spectrum ($CDCl_3$) of **8** showed doublets at δ 5.28 ($J_{3,4}$ 6.9 Hz) and δ 4.06 ($J_{4,5}$ 8.2 Hz) for H-3 and H-5 respectively. H-4 appeared as a doublet of doublets at δ 4.30 ($J_{3,4}$ 6.9, $J_{4,5}$ 8.2 Hz). The isoxazolidine ring carbons appeared at δ 76.42 (C-3), δ 68.19 (C-4) and δ 81.80 (C-5); the keto-carbonyl appeared at δ 197.04. From a comparison of chemical shifts of the isoxazolidine ring protons and coupling constants, as well as the ^{13}C NMR shifts with those of similar cycloadducts[5f], it was established that the cycloadduct has structure 3,4-*trans*-4,5-*trans*-2-methyl-3-(1-naphthyl)-5-phenyl-4-oxophenyl isoxazolidine (**8**).

[3+2] Cycloadditions with *C*-phenyl-*N*-benzyl nitrone, 9

C-phenyl-*N*-benzyl nitrone (**9**), m.p. 118°C, was prepared according to the method of Coşkun *et al.*[10]. 32CAs of *C*-phenyl-*N*-benzyl nitrone were studied with four dipolarophiles, *viz*. the dimethyl arylidene malonates (**5**, **10**, **11**) and methyl cinnamate (**15**) (Scheme II).

The reactions were carried out in refluxing anhydrous toluene (~110°C) under nitrogen atmosphere for 16 hours with 1:3 molar ratio (dipole: dipolarophile) of the reactants. The reactions were monitored by TLC and 300 MHz ^{1}H-NMR analysis of aliquots removed from time to time. The reactions were worked up by removal of solvent under reduced pressure in a Büchi rotary evaporator (the crude post-reaction mixture was analysed by TLC and ^{1}H-NMR) followed by chromatography over neutral alumina. ^{1}H-NMR analysis of the post-reaction mixture for the reactions of 9 with the dimethyl arylidene malonates (5, 10, 11) showed presence of only one product, *viz.* (12, 13, 14), in each reaction.

Reaction of *C*-phenyl-*N*-benzyl nitrone (**9**) with dimethyl 4-nitrobenzylidene malonate (**10**) gave cycloadduct **13**, $C_{26}H_{24}N_2O_7$, m.p. 138°C (yield 84%), as the sole product. Structure of cycloadduct **13** was suggested to be 3,5-*trans*-2-benzyl-3-phenyl-5-(4'-nitrophenyl)-4,4-dicarbmethoxy isoxazolidine, $C_{26}H_{24}N_2O_7$ by detailed spectroscopic studies, and confirmed by XRD analysis. The UV (MeOH) spectrum of **13** showed a peak at 276 nm (log ε 3.76). Its IR spectrum (KBr) showed strong absorption band at 1728 cm^{-1} for an unconjugated carbonyl group; medium intensity bands at 822 cm^{-1} and at 749 cm^{-1} for presence of 1,4-disubstituted benzene ring and monosubstituted benzene ring(s) respectively. Characterisation of the structure of this cycloadduct was achieved by analysing its NMR spectra. Its 300 MHz ^{1}H NMR spectrum showed singlets at δ 5.01 (H-3) and δ 6.13 (H-5). The isoxazolidine ring carbons appeared at δ 76.12 (C-3), δ 74.89 (C4) and δ 82.77 (C-5). The two quaternary carbonyl carbons appear at δ 163.68 and δ 168.06. From a comparison of chemical shifts of the isoxazolidine ring protons and carbons, with those of similar cycloadducts[6], it seemed apparent that the product has structure 3,5-*trans*-2-benzyl-3-phenyl-5-(4'-nitro) phenyl-4,4-dicarbmethoxy isoxazolidine (**13)** with the H-3 and H-5 *trans* to each other. The assignments were confirmed by ^{1}H-^{1}H COSY 45°.

The structure and stereochemistry of cycloadduct **13** was confirmed by XRD analysis. **13** was recrystallised by slow evaporation from methanol solution at room temperature to obtain single crystals. Diffraction data were recorded on a Bruker Smart

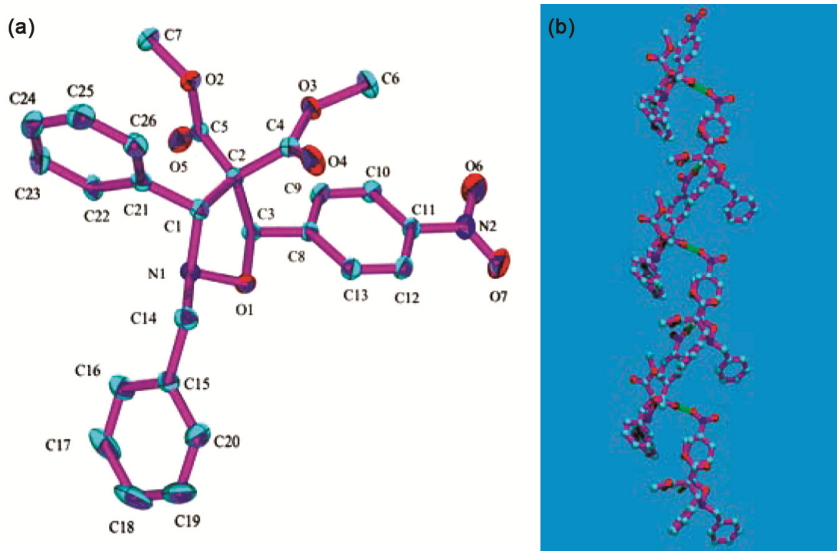


Figure 4 — (a) Structure and stereochemistry of cycloadduct (13) derived from single crystal XRD studies. (b) One-dimensional supramolecular helical chain structure

Apex II CCD area detector diffractometer operating the Mo Kα radiation (λ = 0.7107 Å). The projections are shown in Figure 4 (a and b) and Figure 5. The numberings of structures as given in these projections are those provided in the X-ray crystallographic analysis outputs. The crystallographic parameters of **13** are as follows: Space group Monoclinic P21/c (Z=2), with cell parameters: a, 9.3037(3) Å; b, 18.6853(5) Å; c, 13.9615(4) Å; α, 90°; β, 104.065(1)°; γ, 90°. The XRD study (Figure 4a) showed an all *trans*- configuration: H-3 and H-5 were *trans*-oriented; additionally, the N-lone pair was *trans*- to H-3.

The crystal structure proved very interesting. One-dimensional supramolecular helical chain structure was present, as shown in Figure 4b. Three-dimensional supramolecular structure formed through hydrogen bonding, π…π interaction and C-H…π interactions in the crystalline structure is shown in Figure 5.

Reaction of **9** with a three-molar excess of dimethyl benzylidene malonate **5** in refluxing anhydrous toluene under nitrogen for 16 hours, furnished a single cycloadduct **12**. This was purified by chromatography over neutral alumina as pale yellow crystals, m.p. 132-135°C. Its IR spectrum (KBr) showed bands at 1725 cm^{-1} (ester carbonyl), and 748, 638 cm^{-1} (mono-subtituted benzene ring). Characteristic signals in the 300 MHz ^{1}H NMR spectrum of **12** were the isoxazolidine ring H-3 and H-5 singlets at δ 4.93 and δ 6.04 respectively; the

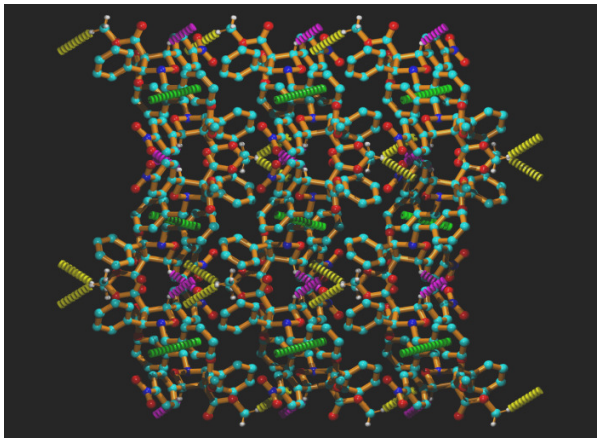


Figure 5 — The three - dimensional supramolecular structure formed through hydrogen bonding (magenta color), π…π interaction (green color) and C-H…π interactions (yellow color) in the cycloadduct 13

benzyl protons at δ 3.80 and δ 3.77; the methoxy protons at δ 2.27 and δ 3.00. In the 75.5 MHz ^{13}C NMR the isoxazolidine ring carbons resonated at δ 77.41 (C-3), δ 74.85 (C4) and δ 82.73 (C-5); the carbonyl carbons at δ 163.64 and δ 165.91; the benzyl carbon at δ 59.39.

Similarly, reaction of **9** with **11** in refluxing toluene yielded **14** as the sole product. Its IR spectrum (KBr) showed absorption bands at 1728 cm^{-1} (unconjugated carbonyl group), 822 and 749 cm^{-1} (1,4-disubstituted benzene ring and monosubstituted benzene ring respectively). 300 MHz ^{1}H NMR spectrum of adduct **14** showed singlets at δ 4.97 and δ 6.03 for H-3 and

H-5 respectively of the isoxazolidine ring. The isoxazolidine ring carbons appeared at δ 76.08, δ 74.85 and δ 82.73 corresponding to C-3, C4 and C-5 respectively; the benzyl carbon resonated at δ 59.40.

Similarity in ^{1}H NMR chemical shifts and coupling constants, and ^{13}C NMR chemical shifts of **12** and **14** with those of **13**, allowing for the substituent changes in ring C of the cycloadducts, confirmed the identity of the regiochemistry and stereochemistry of these as 3,5-*trans*-2-benzyl-3,5-diphenyl-4,4-dicarbmethoxy isoxazolidine (**12**) and 3,5-*trans*-2-benzyl-3-phenyl-5-(4'-chloro phenyl)-4,4-dicarbmethoxy isoxazolidine (**14**).

Reaction of *C*-phenyl-*N*-benzyl nitrone (**9**) with a three-molar excess of methyl cinnamate (**15**) was carried out in refluxing toluene for 16 hours. A single cycloadduct **16**, $C_{24}H_{23}NO_3$, was obtained by chromatography over neutral alumina as pale yellow crystals, m.p. 118-120°C (72%) from 10% benzene in petroleum ether eluates. 300 MHz ^{1}H NMR spectrum of the cycloadduct **16** showed doublets at δ 5.35 (d, J = 8.1Hz) and δ 4.27 (d, J = 8.1Hz) assignable respectively to H-3 and H-5 of the isoxazolidine ring, H-4 resonated at δ 3.37 as a triplet (J = 8.1Hz). The benzyl protons appeared as a close coupled AB system at δ 3.80 and δ 3.77. In its 75.5 MHz ^{13}C-NMR spectrum, the non-aromatic methine carbons appeared at δ 70.72 (C-3), δ 65.17 (C4) and δ 80.58 (C-5). The quaternary carbonyl carbon appeared at δ 171.63; the benzyl and methyl carbons resonated at δ 59.62 and 51.05 respectively. From a comparison of chemical shifts and coupling constants of the isoxazolidine ring protons, with those of similar cycloadducts [2a, 5e], the structure 3,4-*trans*-4,5-*trans*-2-benzyl-3,5-diphenyl-4-carbmethoxy isoxazolidine (**16**) could be established for the product.

Computational Studies

Prediction of reactivity and selectivity

Computational studies were performed by Density Functional Theory with Becke's[11] three parameter hybrid exchange functional in combination with the gradient-corrected correlation functional of Lee, Yang and Parr[12] using 6-311++ G(d,p) basis set. All calculations were carried out using Gaussian 2003 set of Programs[13] along with the graphical interface Gauss View 2003.

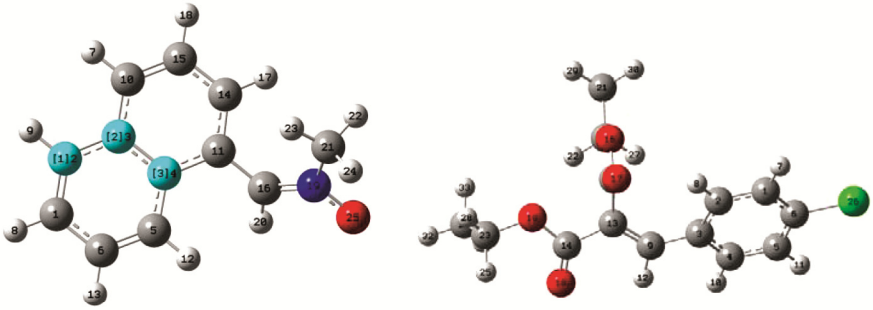
The optimised molecular geometries of nitrone 1, and dipolarophiles 2, 5, 7, 10 are given in Figure 6; the optimised molecular geometry of nitrone 9 is given in Figure 7.

The computed molecular geometry of nitrone **1** (dipole moment: 3.01 Debye) showed that it has a near planar structure, with the naphthyl ring and nitrone functionality in one plane. The dipolarophile benzylidene acetone (**7**) has a planar structure. The computed molecular geometries of several α,β-unsaturated ester dipolarophiles, including methyl cinnamate and aryl benzylidene malonates have been discussed in one of our earlier publications[7e]. In this publication we had presented the computed molecular geometry of dimethyl benzylidenemalonate (**5**); we had shown that while the phenyl ring and the *trans*-carbomethoxy group are almost coplanar, the second carbomethoxy group (*cis* to the phenyl group) is approximately perpendicular to the rest of the molecular plane, and thus effectively out of conjugation. This was reflected in the difference in bond lengths of the carbonyls, as well as C14-C15 and C14-C16 bonds (numbering as in computational output, Figure 6) of the two carbomethoxyl groups. All the arylidene malonates, whose reactions have been investigated in the present communication have similar molecular geometries, where one of the carboalkoxyl groups is coplanar with the aryl ring, the other is approximately perpendicular to it.

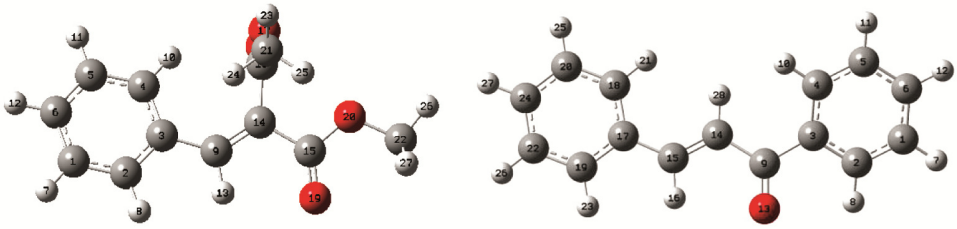
The computed molecular geometry of nitrone 9 (dipole moment: 4.0879 Debye) showed that it has a near planar structure, with the phenyl ring and nitrone functionality in one plane; the phenyl ring of the benzyl group is situated in a plane perpendicular to this.

Merino *et al*[14] have reported that the simplest analysis based upon the charges of the atoms directly involved in the formation of the two new sigma bonds in nitrone cycloaddition reactions can correctly predict the experimental findings. Domingo *et al*[15] have reported theoretical studies on the regioselectivity of 1,3-dipolar cycloaddition reactions using DFT based reactivity indices. He concluded that the regioselectivity can be consistently explained by the most favourable interactions between the highest nucleophilic site of one reactant with the highest electrophilic site of the other.

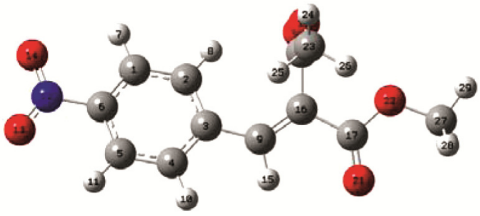
The global properties[4a,7 ,15 ,16], *i.e.* electronic chemical potential (μ), global hardness (η), global softness (S) and global electrophilicity indices (ω) were computed at DFT/B3LYP/6-311++G(d,p) level of theory for the reactants reported in the present communication (Table I): electronic chemical potential $\mu \approx (\varepsilon_H + \varepsilon_L)/2$; global hardness $\eta \approx (\varepsilon_L - \varepsilon_H)$,



C-(1-Naphthyl)-*N*-Methyl Nitrone (1) Diethyl 4-Chlorobenzylidene Malonate **2**



Dimethyl Benzylidene Malonate (5)[7c] Benzylidene acetophenone 7



Dimethyl 4-Nitrobenzylidene Malonate **10**

Figure 6 — Computed Molecular Geometry of *C*-(1-Naphthyl)-*N*-Methyl Nitrone **1** and Dipolarophiles (**2**, **5**, **7**, **10**) – numbering according to computational output.

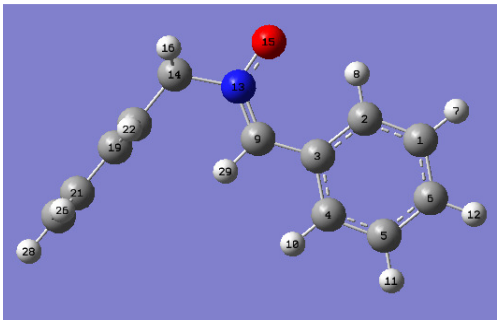


Figure 7 — Computed Molecular Geometry of *C*-Phenyl-*N*-Benzyl Nitrone **9** – numbering according to computational output

where ε_H and ε_L are the one-electron energies of the HOMO and LUMO. Global softness S is given by the inverse of 2η; the global electrophilicity indices are expressed by $\omega \approx \mu^2/2\eta$. The calculation of Fukui functions of an atom in a molecule proves to be a useful criterion to characterise the reactive sites within a chemical species. A high value of the Fukui function implies a high reactivity of the site. The Fukui functions can be written in terms of respective electron populations computed from Natural Population Analysis (NPA) of the cationic $[q_k(N-1)]$, neutral $[q_k(N)]$ and anionic $[q_k(N+1)]$ systems. For nucleophilic attack: $f_k^+ = q_k(N+1) - q_k(N)$; whereas for electrophilic attack: $f_k^- = q_k(N) - q_k(N-1)$. The local electrophilicity index ω_k is expressed as $\omega_k = \omega f_k^+$, where f_k^+ is the Fukui function for nucleophilic attack, and ω is the global electrophilicity index.

The HOMO/LUMO energy gaps for the 32CAs of *C*-(1-naphthyl)-*N*-methyl nitrone (**1**) to the dipolarophiles (**2, 5, 7**), and of the 32CAs of *C*-phenyl-*N*-benzyl nitrone (**9**) to the dipolarophiles (**5, 10, 11, 15**) are listed in Table II. The $LUMO_{Dipolarophile}$-$HOMO_{Dipole}$ gaps are smaller than the $LUMO_{Dipole}$-$HOMO_{Dipolarophile}$ interaction energies. Hence the former will be the predominant interaction in each case, this reveals a normal electron demand

Table I — DFT/B3LYP/6-311++G(d,p) computed frontier orbital energies, electronic chemical potential (μ), global hardness (η) and global electrophilicity indices (ω) of nitrones 1 and 9 and dipolarophiles 2, 5, 7, 10, 11 and 15 (values in eV)

Compd	HOMO (ev)	LUMO (ev)	μ (ev)	H (ev)	S (ev)	ω (ev)
C-(1-naphthyl)-*N*-methyl nitrone (**1**)	-5.877	-2.041	-3.959	3.836	0.1304	2.044
C-Phenyl-*N*-Benzyl Nitrone (**9**)	-5.850	-1.605	-3.727	4.245	0.1178	1.636
Diethyl 4-Chlorobenzylidene Malonate (**2**)	-6.857	-2.476	-4.666	4.381	0.1141	2.284
Dimethyl Benzylidene Malonate (**5**)[7c]	-6.884	-2.394	-4.639	4.490	0.1113	2.395
Benzylidene Acetophenone (**7**)	-6.692	-2.503	-4.597	4.189	0.1194	2.523
Dimethyl 4-Nitrobenzylidene Malonate (**10**)	-7.537	-3.428	-5.482	4.109	0.1217	3.657
Dimethyl 4-Chlorobenzylidene Malonate (**11**)	-6.857	-2.576	-4.716	4.281	0.1168	2.598
trans-Methyl Cinnamate (**15**)[7e]	-6.748	-2.150	-4.449	4.598	0.1087	2.152

Table II — Computed energy differences between the two possible HOMO/LUMO interactions for the dipole and the dipolarophiles (values in eV)

Reactions	$LUMO_{Dipolarophile}$ - $HOMO_{Dipole}$ (eV)	$LUMO_{Dipole}$ - $HOMO_{Dipolarophile}$ (eV)	{($LUMO_{Dipole}$ -$HOMO_{Dipolarophile}$) - ($LUMO_{Dipolarophile}$ -$HOMO_{Dipole}$)} (eV)
Nitrone (**1**) + Diethyl 4-Chlorobenzylidene Malonate (**2**)	3.401	4.816	1.415
Nitrone (**1**) + Dimethyl Benzylidene Malonate (**5**)[7c]	3.483	4.843	1.360
Nitrone (**1**) + Benzylidene Acetophenone (**7**)	3.374	4.651	1.277
Nitrone (**9**) + Dimethyl Benzylidene Malonate (**5**)[7c]	3.456	5.279	1.823
Nitrone (**9**) + Dimethyl 4-Nitrobenzylidene Malonate (**10**)	2.422	5.932	3.51
Nitrone (**9**) + Dimethyl 4-Chlorobenzylidene Malonate (**11**)	3.274	5.252	1.823
Nitrone (**9**) + *trans*-Methyl Cinnamate (**15**)	3.727	4.707	0.980

Table III — Computed values of condensed Fukui functions, $f_k^+ f_k^-$, and the local electrophilicity indices ω_k^+ of *C*-(1-naphthyl)-*N*-methyl nitrone (1), *C*-phenyl-*N*-benzyl nitrone (9), dimethyl benzylidene malonate (5) and methyl cinnamate (15)

Compd	k	f_k^+	f_k^-	ω_k^+ (eV)
C-(1-Naphthyl)-*N*-methyl nitrone (**1**)	O_{25}	0.1252	0.2524	0.2463
	C_{16}	0.0227	0.1215	0.0447
C-Phenyl-*N*-Benzyl Nitrone (**9**)	O_{15}	0.0180	0.400	0.0295
	C_9	0.191	0.062	0.314
Dimethyl benzylidene malonate (**5**)	C-β	0.148	0.140	0.359
	C-α	0.111	0.187	0.2694
trans-Methyl cinnamate (**15**)	C- β	0.131	0.0103	1.633
	C- α	0.129	0.0101	1.932

character of these cycloaddition reactions. The differences {($LUMO_{Dipole}$ -$HOMO_{Dipolarophile}$) - ($LUMO_{Dipolarophile}$ -$HOMO_{Dipole}$)}vary significantly, but not enough to affect the overall nature of the process as normal electron demand cycloadditions.

Theoretical analysis of the regioselectivities of 32CAs of *C*-(1-naphthyl)-*N*-methyl nitrone (**1**) and *C*-phenyl-*N*-benzyl nitrone (**9**) have been carried out in terms of local electrophilicity indices ω_k^+ and the condensed Fukui functions for the electrophilic attack f_k^-. These are given along with those of dipolarophiles (**5**) and (**15**) in Table III.

For *C*-(1-naphthyl)-*N*-methyl nitrone (**1**), the oxygen has higher f_k^- compared to the carbon atom. In case of dipolarophiles, *e.g.* dimethyl benzylidene malonate (**5**), C_β has the higher local electrophilicity index ω_k^+ than that of C_α. Therefore C_β of the dipolarophile **5** will become linked to the oxygen atom of the nitrone following favourable interaction between the highest nucleophilic and electrophilic sites of the respective reactants. This predicts generation of the 4,4-dicarbomethoxy substituted isoxazolidine (**6**) from 32CA of (**1**) with (**5**).

Similar considerations hold for 32CAs of dipole *C*-phenyl-*N*-benzyl nitrone (**9**). The oxygen in (**9**) has higher f_k^- compared to the carbon atom. In dipolarophile dimethyl benzylidene malonate (**5**), C_β has the higher local electrophilicity index ω_k than that of C_α. nucleophilic and electrophilic sites of the two reactants. Hence, C_β of the dipolarophile will be linked to the oxygen atom of nitrone (**9**) following favourable interaction between the highest

nucleophilic and electrophilic sites of the two reactants; the 4,4-dicarbomethoxy substituted isoxazolidine (**12**) is thus predicted to be generated preferentially from 32CA of (**9**) with (**5**). In methyl cinnamate, C_β has the higher local electrophilicity index ω_k than that of C_α. This predicts preferential generation of 4-carbomethoxy substituted isoxazolidines from 32CA of (**9**) with (**15**).

These results can be generalised for all the [3+2] cycloadditions reported in the present communication. The predominant pathway in these is predicted to be that in which cycloadduct with the electron-withdrawing carbonyl group(s) is in the 4-position. These predictions are in complete agreement with the experimental studies.

The theoretical rationalisations of the regioselectivities of 32CAs of *C*,*N*-diaryl nitrones and *C*-aryl-*N*-methyl nitrones, where the aryl groups were phenyl/ substituted phenyl and the rationalisation of the reaction course, were discussed earlier by us[2a,4a,7]. The present theoretical studies for 32CAs of (**1**) and (**9**), where the *C*-phenyl group has been replaced by 1-naphthyl group, and the *N*-methyl group has been replaced by benzyl group respectively, predict similar regioselectivities to the earlier reaction series. These are excellently corroborated by our experimental results on all 32CAs of the *C*,*N*-disubstituted nitrones investigated by us so far[2,4,5,6,7].

Experimental Section

General

Melting points were recorded on an electrically heated Köfler Block apparatus and are uncorrected. All chemicals were procured from E. Merck. Column and thin layer chromatography were carried out using neutral alumina and silica gel G respectively. Spots on TLC chromatograms were visualised with iodine vapour. Anhydrous sodium sulphate was used for drying extracts. Petrol refers to petroleum ether AR (b.p. 60-80°C). Analytical samples were routinely dried over anhydrous $CaCl_2$ *in vacuo* at room temperature. Elemental analysis (C, H, N) were conducted using the Perkin-Elmer 2400 series II elemental analyser, and their results were found to be in good agreement (±0.2%) with the calculated values for C, H, and N. IR spectra were recorded in KBr discs on Perkin-Elmer FT-IR model RX-9. UV spectra were recorded with a Hitachi UV-Vis-NIR model U3501. Mass spectra were recorded with a JEOL JMS600 Mass spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) were recorded in $CDCl_3$ solution with a Bruker AM-300L and Avance 300 instruments in $CDCl_3$ (chemical shifts in δ ppm and *J* in Hertz). 75.5 MHz ^{13}C NMR signals for the non aromatic methine carbons, aromatic CHs, quaternary aromatic carbons and the carbonyl carbon in the compounds were assigned by comparing fully decoupled and DEPT 135° spectra. Assignments of aromatic carbons were done on the basis of intercomparison with similar cycloadducts[5e,5f,6], use of additivity parameters[17] and SDBS values[18].

X-ray data of **3** and **13** have been deposited at the Cambridge Structural Data Centre under CCDC numbers **CCDC787240** and **CCDC793462** respectively. The data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif or by e-mailing data_request@ccdc. cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK.

Supplementary data

Supplementary Data - 1

Spectra of *C*-(1-naphthyl)-*N*-methyl nitrone (1). Spectra and X-Ray parameters of cycloadduct 3,5-*trans*-2-methyl-3-(1-naphthyl)-5-(4'-chlorophenyl)-4,4-dicarbethoxy isoxazolidine (3). Spectra of cycloadducts 6 and 8.

Supplementary Data - 2

Computational calculations (DFT) pertaining to *C*-(1-naphthyl)-*N*-methyl nitrone (1), and dipolarophiles reacting with it.

Supplementary Data - 3

Spectra and X-Ray parameters of cycloadduct 13. Spectra of cycloadducts 12, 14, 16.

Supplementary Data - 4

Computational calculations pertaining to *C*-phenyl-*N*-benzyl nitrone (9), and dipolarophiles reacting with it.

Preparation of the starting materials

Preparation of nitrones

***C*-(1-Naphthyl)-*N*-methyl nitrone, 1**: 1-Naphthaldehyde (1.855g., 11.9 mmole) and N-methyl hydroxylamine hydrochloride (0.943g., 14.3 mmole) were taken with a large excess of anhydrous $NaHCO_3$ (1.85g., 22.5 mmole) in anhydrous CH_2Cl_2 (20 ml) and subjected to microwave irradiation (~1000W) for 12 min., following the procedure developed earlier by

us. The reaction mixture was filtered, evaporation of the solvent from the filtrate gave **1** (2.113g. 96% yield). **1** crystallised as needles, m.p. 94ºC (hexane-$CHCl_3$ 1:1). IR $(KBr)_{max}$, cm^{-1}: 3101, 3054, 2927, 2848 (w, naphthyl ring), 1593 (m, C=N), 1510 (s, C=C), 1184 (m, N-O), 857, 771, 687 (aromatic CH). ^{1}H NMR, δ: 8.09 (s, nitrone CH), 3.96 (NMe), 9.41 (d 7.5, H-8), 7.94 (d 8.1, H-2), 7.79-7.85 (m ovl., H-4, H-5), 7.42-7.52 (m ovl., H-3, H- 6, H-7). Anal.: Calcd. for $C_{12}H_{11}NO$: C, 77.8; H, 6.0; N, 9.7%; Found C, 77.6; H, 6.1; N, 9.6%.

C-phenyl-*N*-benzyl nitrone (**9**) was prepared according to the literature method of Coşkun[10].

Preparation of Dipolarophiles

The arylidene malonate dipolarphiles (**2**, **5**, **10**, **11**) were prepared by standard experimental procedures[19,20,21] from dimethyl/diethyl malonates by condensation with the appropriate aromatic aldehydes in presence of piperidine in benzene solution. Their structural integrities were confirmed by IR and NMR spectra. Benzylidene acetophenone (**7**) was obtained by literature method[22].

General procedure for [3+2] cycloaddition

The reactions of the nitrones (**1**) and (**9**) with threefold molar proportion of the dipolarophile were carried out in refluxing thiophene-free anhydrous toluene (~110°) under nitrogen. The crude reaction mixtures were concentrated in a Büchi rotary evaporator to remove the solvent. The residues were analysed by TLC and 300 MHz ^{1}H-NMR. Yields and product ratios were estimated by integration of relevant ^{1}H-NMR signals. The crude reaction products were chromatographed over neutral alumina to obtain the products.

[3+2] Cycloadditions of *C*-(1-naphthyl)-*N*-methyl nitrone (1)

3,5-*trans*-2-methyl-3-(1-naphthyl)-5-(4'-chlorophenyl)-4,4-dicarboethoxy isoxazolidine, $C_{26}H_{26}NO_5Cl$, (3). (**1**) (0.85 g., 0.0044 mole) refluxed with diethyl 4-chloro-benzylidene malonate (**2**) (3.38 g., 0.0132 mol) for 10 hr. ^{1}H-NMR analysis of crude product showed presence of two cycloadducts **3** (88%) and **4** (4%) (total yield 92%). Chromatography over neutral alumina afforded **3** in the hexane: ethyl acetate (4:1) eluates. **3**: Crystals from hexane-chloroform (1:1), m.p. 108°C, R_f 0.49 (silica gel G, benzene). Anal.: Calcd. for $C_{26}H_{26}NO_5Cl$: C, 66.7; H, 5.6; N, 3.0%; Found C, 66.6; H, 5.6; N, 3.0%. UV λ_{max} (MeOH) 225, 277 nm (log ε 4.22, 3.84); IR (KBr) ν_{max} (cm^{-1}): 2979, 2925 (m), 1721 (s, carbonyl), 1482, 1256, 1200 (m, aromatic C=C), 1370 (m, methyl), 1102 (m, aromatic C-Cl), 791, 705, 637 (m, aromatic rings). ^{1}H NMR: δ 5.54 (s, H-3), 6.05 (s, H-5), 2.76 (s, N-CH_3), 2.79 & 3.32 (m, $CO_2CH_2CH_{3(I)}$), 0.00*(t, J = 7.2 Hz, $CO_2CH_2CH_{3(I)}$), 3.24 & 3.74 (m, $CO_2CH_2CH_{3(II)}$), 0.61 (t, J = 7.1 Hz, $CO_2CH_2CH_{3(II)}$), 8.18 (d, J = 8.4 Hz, H-8), 7.38-7.51 and 7.69-7.81 (m, 6H, *naphthyl ring*; of which 7.41, H-7 and 7.76, H-6 assigned from COSY cross-peaks), 7.25 and 7.31 (d each, J = 8.7 Hz, *C*/H-2,6 and *C*/H-3,5 - close coupled AB system). ^{13}C NMR: δ 73.48 (C-3), 74.91 (C-4), 83.58 (C-5), 43.18 (N-CH_3), 168.30 & 167.90 ($CO_{(I,\ II)}$), 60.81 and 61.65 ($CO_2CH_2CH_{3(II)}$ and $CO_2CH_2CH_{3\ (I)}$), 12.37 ($CO_2CH_2CH_{3\ (I)}$), 13.18 ($CO_2CH_2CH_{3(II)}$); 128.55, 128.55, 128.44, 126.35, 125.48, 125.33, 123.82 (*naphthyl ring A*,*B*/C-2,3,4,5,6,7,8); 128.55, 128.13 (*C*/C-2,6,3,5); 134.21, 134.11, 133.49, 132.99 (*naphthyl ring A*,*B*/C-1,9,10; *C*/C-1), 128.92 (*C*/C-4).

X-ray crystallographic analysis of 3

Cycloadduct **3** was recrystallised by slow evaporation from hexane-chloroform (1:1) solution (100 µl) at room temperature to obtain single crystals. XRD studies were carried out with selected crystals mounted in cryo-loops and stored at 100°K in liquid nitrogen. Diffraction data were recorded on a NONIUS KAPPA CCD diffractometer operating the Mo Kα radiation (λ = 0.7107 Å). The LURE DC1 synchrotron facility in Orsay, France was used to record the data. An Image Plate system (MAR 345) was used as the detector. Recordings were done under cryotemperature conditions at -50^{0}C. The structures were solved by direct methods (SHELXS) and refined using isotropic, then anisotropic thermal factors (SHELXL program)[23]. Hydrogens were gradually introduced in the calculations and kept riding on the bonded atom during all refinements. Figures are drawn using the PLATON program[24].

CCDC reference no.: CCDC 787240. $C_{26}H_{26}$ Cl NO_5, Formula Wt. 476.9; Space group Triclinic P-1, Z 2. Parameters: a, 7.691(1) Å; b, 12.639(1) Å; c, 13.260(1) Å; α, 114.80(5)°; β, 99.30(4)°; γ, 91.76(5)°; Volume(Å^3) 1147.6(1). No. of independent F 2476; No. of obs. F 2292; Completeness (%) 75.2; Resolution limits (Å) 8-0.90.

Supplementary data for **3** (***Supplementary data 1***) contain - Positional parameters (x10^4) and mean recalculated isotropic factors (x10^3) for non-hydrogen atoms; Positional parameters (x10^3) and mean

recalculated isotropic factors ($x10^3$) for hydrogen atoms; Anisotropic thermal parameters ($x10^3$) for non-hydrogen atoms; Bond distances (Ångstrom) for non-hydrogen atoms; Bond angles (degrees) for non-hydrogen atoms.

3,5-*trans*-2-Methyl-3(1-naphthyl)-5-phenyl-4,4-dicarbomethoxy isoxazolidine, $C_{24}H_{23}NO_5$, (6): Nitrone **1** (0.85 gm, 0.0044 mol) refluxed with dimethyl benzylidene malonate (**5**) (3.46 gm, 0.0132 mol) in toluene (~110°C) for 10 hr. ^{1}H-NMR analysis of the post-reaction mixture showed presence of only one product **6** (conversion 90%). **6** was obtained in hexane:ethyl acetate (9:1) eluates by chromatography over neutral alumina. Recrystallisation from hexane-chloroform (1:1) gave colourless crystals, m.p.102ºC. Anal. Calcd. for $C_{24}H_{23}NO_5$: C, 71.1; H, 5.7; N, 3.5%; Found C, 70.9; H, 5.8; N, 3.4%. IR (KBr) ν_{max} (cm^{-1}): 2957 (m), 1727 (s, carbonyl), 1444, 1260 (m, aromatic C=C), 1365 (m, methyl), 852, 811, 751, 692 (m, aromatic rings). EI-MS (70eV) 405 (M^+), 374 (M-OMe), 330 (M-CO_2Me), 185 (cycloreversion), 141, 105, 91, 77 (base peak). ^{1}H NMR: δ 4.64 (s, H-3), 5.95 (s, H-5), 2.76 (s, N-C*H*$_3$), 3.07 (s, $CO_2CH_{3(I)}$), 3.78 (s, $CO_2CH_{3(II)}$), 7.20-7.35 (*naphthyl ring*/H-2,3,4,5,6,7; *C*/H-2,6,3,5,4), 8.15 (d, *J* = 7.8Hz, *naphthyl ring*/H-8). ^{13}C NMR: δ 77.87 (C-3), 75.34 (C-4), 84.03 (C-5), 42.96 (N-CH_3), 167.22 & 168.43 ($CO_{(I, II)}$), 52.16 & 52.66 ($CO_2CH_{3\ (I)}$ & $CO_2CH_{3\ (II)}$), 130.68, 128.56, 128.60, 128.87, 128.56, 128.60, 127.30, 129.37 (*naphthyl ring A*,*B*/C-2,3,4,5,6,7,8; ***C***/ C-4), 134.49, 134.24, 132.76, 135.71 (*naphthyl ring A*,*B*/C-1,9,10; ***C***/C-1), 127.30 (*C*/C-2,3,5,6).

3,4-*trans*-*4,5*-*trans*-2-Methyl-3-(1-naphthyl)-5-phenyl-4-oxophenyl isoxazolidine, $C_{27}H_{23}NO_2$, (8): Nitrone **1** (0.85 gm, 0.0044 mol) refluxed with a three-molar excess of benzylidene acetophenone (**7**) (2.75 gm, 0.0132 mol) for 12 hr. ^{1}H-NMR analysis of crude product showed presence of only one cycloadduct **8** (conversion 62%). Purification by chromatography over neutral alumina gave **8,** m.p. 94ºC, in hexane:ethyl acetate (3:1) eluates. Anal.: Calcd. for $C_{27}H_{23}NO_2$: C, 81.4; H, 7.1; N, 3.5%; Found C, 81.1; H, 7.3; N, 3.6%. IR (KBr) ν_{max} (cm^{-1}): 3057 (m), 1659 (s, conjugated ketone carbonyl), 1599, 1494 (m, aromatic C=C), 1337 (m, methyl), 744, 683 (m, aromatic rings). ^{1}H NMR: δ 5.28 (d, *J* = 6.9 Hz, H-3), 4.30 (dd, *J* = 6.9, 8.2 Hz, H-4), 4.06 (d, *J* = 8.2 Hz, H-5), 2.60 (N-CH_3), 7.00-7.55 (m, ovl., *naphthyl ring A*,*B*/H-2,3,4,5,6,7,8), 7.85 (d, *J* = 7.1Hz,1H), 7.26-7.33 (m, ovl., **C**/H-2,6,3,5,4). ^{13}C NMR: δ 76.42 (C-3), 68.19 (C-4), 81.80 (C-5), 43.24 (N-CH_3), 197.04 (-CO-), 126.03, 127.67, 127.86, 128.35, 128.17, 128.13, 128.60 (*naphthyl ring A*,*B*/C-2,3,4,5,6,7,8); 134.54, 134.54, 133.48 (*naphthyl ring A*,*B*/C-1,9,10); 137.85 (*C*/C-1), 130.49 & 130.18 (*C*/C-2,6), 132.43 &133.31 (*C*/C-3,5), 128.27 (*C*/C-4).

[3+2] Cycloadditions with C-phenyl-N-benzyl nitrone (9)

3,5-*trans*-2-benzyl-3,5-diphenyl-4,4-dicarbomethoxy isoxazolidine, $C_{26}H_{25}NO_5$, (12): Reaction of **9** (0.93 gm, 0.0044 mol) with dimethyl benzylidene malonate (**5**) (3.46 gm, 0.0132 mol); refluxed in toluene under N_2 for 16 hr. ^{1}H-NMR analysis of the crude product showed the presence of single cycloadduct **12**, which was isolated by chromatography over neutral alumina in the *n*-hexane eluates as pale yellow crystals, m.p. 132-135°C (78%), R_f 0.59 (silica gel G, benzene). Anal.: Calcd. for $C_{26}H_{25}NO_5$: C, 72.4; N, 3.2; H, 5.8 %; Found C, 72.2; N, 3.4; H, 5.8 %. IR (KBr) ν_{max} (cm^{-1}): 1725 (s, ester carbonyl), 1521 (s, C=C), 1259 (s, C-O ester), 748, 638 (m, mono-subtituted benzene ring). ^{1}H NMR ($CDCl_3$): δ 4.93 (s, H-3), 6.04 (s, H-5), 3.77 & 3.80 (d, 1H AB system, *J* = 17.8 Hz, C*H*$_2$Ph), 3.00 (two OMe), 7.14-7.52 (m, ovl., 15H, *aromatic protons of ring A*, *B*, *C*). ^{13}C NMR: δ 76.08 (C-3), 74.85 (C-4), 82.73 (C-5), 52.93 & 52.85 (each CO_2CH_3), 168.01 & 167.95 (two C=O), 59.39 (*C*H$_2$Ph), 135.72 & 136.69 (*A*/C-1,*B*/C-1), 128.78, 128.62,128.46, 128.18, 128.11 (*A*/2,6,3,5; *B*/2,6,3,5; *C*/3,5); 127.31 (*A*/4), 129.83 (*B*/4), 139.03 (C/1), 129.21 (*C*/2, 6), 123.91 (*C*/4).

3,5-*trans*-2-Benzyl-3-phenyl-5-(4'-nitro) phenyl-4,4-dicarbomethoxy isoxazolidine, $C_{26}H_{24}N_2O_7$, (**13**): 9 (0.93 gm, 0.0044 mol) with dimethyl 4-nitro-benzylidene malonate (**10**) (3.50 gm, 0.0132 mol) refluxed in toluene under N_2 for 16 hr**.** ^{1}H-NMR analysis of crude post-reaction mixture showed the presence of single cycloadduct **13**. It was purified by chromatography over neutral alumina in ethyl acetate: hexane (1:4) eluates crystallizing as pale yellow crystalline needles from methanolic chloroform, m.p. 136-138°C (yield 84%). R_f 0.49 (silica gel G, benzene). Anal.: Calcd. for $C_{26}H_{24}N_2O_7$: C, 65.5; N, 5.9; H, 5.0%; Found C, 65.3; N, 6.0; H, 5.2%. UV λ_{max} (MeOH) 276 nm (log ε 3.76); IR (KBr) ν_{max} (cm^{-1}): 3031 (m), 2954 (m), 2886 (m), 1728 (s, carbonyl), 1601 (m, C=C), 1519, 1344 (m, aromatic -NO_2), 1257 (s, C-O ester), 854 (w, 1,4 disubstituted benzene ring), 745, 694 (w, monosubstituted benzene ring). ^{1}H NMR:

δ 5.01 (s, H-3), 6.13 (s, H-5), 3.08 & 3.05 (each 3H s, -OCH_3), 3.94 & 3.98 (each d, AB system, *J* = 17.7 Hz, CH_2Ph), 7.24-7.55 (10H, m, ovl., *A*/H-2,3,4,5,6; *B*/H-2,3,4,5,6), 7.60 (d, *J* = 8.7, *C*/H-2,6), 8.22 (d, *J* = 8.7, *C*/H-3,5). ^{13}C NMR: δ 76.12 (C-3), 74.89 (C-4), 82.77 (C-5), 52.91 (both OCH_3), 59.43 (CH_2Ph), 168.06 & 168.00 (carbonyl), 147.87 (*C*/4), 143.22 (*C*/1), 135.76 & 136.72 (*A*/1, *B*/1), 128.16, 128.23, 128.78, 128.65, 128.51 (*A*/2,6,3,5; *B*/2,6,3,5; *C*/2,6), 127.36 (*A*/4), 129.86 (*B*/4), 122.99 (*C*/3,5).

X-ray crystallographic analysis of 13

Cycloadduct **13** was recrystallised by slow evaporation from methanol solution at room temperature to obtain single crystals. Diffraction data were recorded on a Bruker Smart Apex II CCD area detector diffractometer operating the Mo Kα radiation (λ = 0.7107 Å) at the Department of Chemistry, University of Calcutta. The structures were solved by direct methods (SHELXS) and refined using isotropic, then anisotropic thermal factors (SHELXL program)[23]. Hydrogens were gradually introduced in the calculations and kept riding on the bonded atom during all refinements. Figures are drawn using the PLATON program[24].

CCDC reference no.: **CCDC793462.** $C_{26}H_{24}N_2O_7$, Formula Wt. 952.94; Space group Monoclinic P21/c, Z 2. Parameters: a 9.3037(3) Å, b 18.6853(5) Å, c 13.9615(4) Å; α 90°, β 104.065(1)°, γ 90°. The X-ray crystallographic study showed an all *trans*-configuration: H-3 and H-5 were *trans*-oriented; additionally the N-lone pair was *trans*- to H-3. The numberings of structures as given in projections in Figures 4a, 4b, 5 as well as in the Tables in the Supplementary Data 3, are those provided in the X-ray crystallographic analysis outputs.

Supplementary data for 13 (***Supplementary data 3***) contain - Crystallographic data, Bond lengths (Å), Bond angles (degrees), torsion angles (degrees), Final Coordinates and Equivalent Isotropic Displacement Parameters of the non-Hydrogen atoms, Hydrogen Atom Positions and Isotropic Displacement Parameters, Hydrogen bond dimensions of 13 in Å.

3,5-*trans*-2-Benzyl-3-phenyl-5-(4'-chloro) phenyl-4,4-dicarbomethoxy isoxazolidine, $C_{26}H_{24}NO_5Cl$, (14): Nitrone **9** (0.93 gm, 0.0044 mol) refluxed with dimethyl 4-chlorobenzylidene malonate (**11**, 3.38 gm, 0.0132 mol) in toluene for 16 hr. ^{1}H-NMR analysis of crude post-reaction mixture, obtained after removal of the solvent in a Büchi rotary evaporator under reduced pressure, showed the presence of single cycloadduct **15**. Product **15** was isolated by chromatography over neutral alumina in ethyl acetate: hexane (1:4) eluates as white crystalline solid, m.p. 140-142°C (76 %); R_f 0.56 (silica gel G, benzene). Anal.: Calcd. for $C_{26}H_{24}NO_5Cl$: C, 67.0; H, 5.2; N, 3.0%; Found C, 67.2; N, 3.1; H, 5.4%. IR (KBr) ν_{max} (cm^{-1}): 3030 (m), 2957 (m), 2851 (m), 1730 (s, C=O), 1518 (s, C=C), 1257 (s, C-O of ester), 1107 (m, aromatic C-Cl), 852 & 812 (m, 1,4 disubstituted benzene ring), 756 & 693 (m, monosubstituted benzene ring). ^{1}H NMR: δ 4.97 (s, H-5), 6.03 (s, H-3), 3.18 and 3.14 (s, 3H each, OMe), 4.05 and 3.90 (d, 1H each, AB system, *J* = 17.8 Hz, -CH_2-), 7.05-7.50 (m, ovl., 15H, Ar-H – *A*,*B*,*C*). ^{13}C NMR: 76.08 (C-3), 74.85 (C4), 82.73 (C-5), 52.92 & 52.13 ($COOCH_3$), 168.01 (both C=O), 59.40 (CH_2), 128.18, 128.37, 128.46, 128.51, 128.59, 128.75 (*A*,*B*,*C*/C-2,6,3,5), 135.74 (*A*/C-1), 136.69 (*B*/C-1), 128.14 (*C*/C-1), 134.19 (*C*/C-4), 127.31 (*A*/C-4), 129.82 (*B*/C-4),128.14 (*C*/C-1).

3,4-*trans*-4,5-*trans*-2-Benzyl-3,5-diphenyl-4-carbomethoxy isoxazolidine, $C_{24}H_{23}NO_3$, (16): Nitrone **9** (0.93 gm, 0.0044 mol) was refluxed with a three-molar excess of **15** (2.140 gm, 0.0132 mol) in toluene for 16 hr. **16** was obtained by chromatography of the crude product over neutral alumina as pale yellow crystals, m.p. 118-120°C (1.180 gm,72%) from hexane-benzene (9:1) eluates. Anal.: Calcd. for $C_{24}H_{23}NO_3$: C, 77.1; H, 6.3; N, 3.8%; Found C, 77.2; H, 6.2; N, 3.8%. ^{1}H NMR: δ 4.27 (d, *J* = 8.1 Hz, H-3), 3.37 (t, *J* = 8.1 Hz, H-4), 5.35 (d, *J* = 8.1 Hz, H-5), 3.45 (s, CO_2Me), 3.80 & 3.77 (d, 1H each, AB system *J* = 17.0 Hz, benzyl CH_2), 7.10-7.50, 7.10-7.50 (m, ovl., 15H, *Ar-H/A*,*B*,*C*). ^{13}C NMR: δ 70.72 (C-3), 65.17 (C-4), 80.58 (C-5), 59.62 (*C*H_2Ph), 171.63 (C=O), 51.15 (CO_2CH_3), 138.07 (*A*/1), 141.54 (*B*/1), 137.12 (*C*/1), 128.62, 128.39 (*B*/4; *C*/4), 129.88 (*A*/4), 128.51, 128.48, 128.76 (*C*/2,6,3,5; *A*/2,6); 127.17,127.37 (*A*/3,5; *B*/2,6), 125.53 (*B*/3,5).

Conclusions

The [3+2] cycloadditions of *C*-(1-naphthyl)-*N*-methyl and *C*-phenyl-*N*-benzyl nitrones to α,β-unsaturated carbonyl compounds as dipolarophiles, *viz*. arylidene malonate esters, methyl cinnamate and benzylidene acetophenone in refluxing toluene were investigated. The intention was to analyse the regio- and stereochemical courses of these reactions. Structure elucidations of the generated cycloadducts were achieved by means of detailed spectroscopic and XRD

studies. All the cycloadditions studied occurred regioselectively to yield tetra/penta-substituted isoxazolidines, where the carbonyl group(s) were attached to the 4-position of the isoxazolidine ring. Computational calculations were carried out at the DFT/B3LYP/6-31++G(d,p) level of theory to analyse the 32CAs studied and to predict the regioselectivities; the predictions were in excellent accord with the experimental results.

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1 This series of publications were previously titled as 1,3-Dipolar Cycloadditions. This is now revised to [3+2] Cycloadditons [32CA], keeping with usage accepted in recent years. The numbering of this series of papers remains unaltered.

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