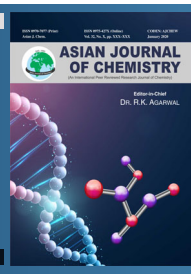
Asian Journal of Chemistry; Vol. 32, No. 8 (2020), 1886-1894

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22695



[3+2] Cycloadditions: Part XXXV. Selective Cycloadditions of *C*-(4-Chlorophenyl)-*N*-methyl Nitrone to Cinnamic Acid Anilides

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Received: 23 February 2020; *Accepted*: 17 April 2020; *Published online*: 27 July 2020; AJC-19963

[3+2] Cycloadditions of nitrones as three-atom components to alkenes yield isoxazolidine cycloadducts, which on chemical transformations can be converted to bioactive compounds. The [3+2] cycloadditions route thus provides conversion of simple natural products to more complex naturally occurring bioactive nitrogen heterocycles, and close analogues. As α,β-unsaturated amides abundantly occur as natural products, [3+2] cycloadditions of nitrones with simpler α,β-unsaturated amides were studied to get information about reactivity profiles. The reactions of *C*-(4-chlorophenyl)-*N*-methyl nitrone as three-atom component to cinnamic acid anilides were investigated. The 3,4-*trans*-4,5-*trans*-4-carboxanilido-2-methyl-3,5-diaryl isoxazolidines were the major cycloadducts; the diastereoisomeric 3,4-*cis*-4,5-*trans*-4-carboxanilido-2-methyl-3,5-diaryl isoxazolidines and regioisomeric 3,4-*trans*-4,5-*trans*-5-carboxanilido-2-methyl-3,4-diaryl isoxazolidines were obtained as minor cycloadducts. The cycloadducts were characterized by NMR studies and XRD analysis.

Keywords: [3+2] Cycloaddition, Isoxazolidine, Nitrone, Cinnamic acid anilides.

INTRODUCTION

[3+2] Cycloadditions offer versatile strategies to generate 5-membered heterocycles [1-8]. Cycloadditions of nitrones to alkenes furnish isoxazolidines, which can be used as templates in the synthesis of different classes of natural products [5-8]. The [3+2] cycloaddition route thus provides conversion of simple natural products to more complex natural occurring bioactive nitrogen heterocycles, and close analogues. Isoxazolidines allow considerable regiochemical and stereochemical control during the cycloaddition process and can be functionalized to a certain extent. Thus it is important to design [3+2] cycloaddition reactions of nitrones to different unsaturated systems with high regio- and stereoselectivity. We have carried out systematic investigations on different aspects of [3+2] cycloaddition of nitrones to various dipolarophiles containing a double bond conjugated with an electron-withdrawing group [7-16]. These include experimental and theoretical studies. α,β-Unsaturated amides occur abundantly as natural products. Considering the easy availability of α,β-unsaturated amides in nature, we have been carrying out a series of studies on [3+2] cycloadditions of different types of nitrones with α,β-unsaturated amides. Two of our recent communications deal with [3+2] cycloadditions of C,N-disubstituted nitrones with cinnamic acid piperidides [9] and cinnamic acid anilides [10], respectively as 2π-components in the cycloaddition process.

The present communication is an extension of our earlier work, and details our investigations on 32CAs of a *C*-aryl-*N*-methyl nitrone to cinnamic acid anilides, as to our knowledge these has not been studied earlier. Structural investigations of the cycloadducts involved detailed NMR studies and X-ray diffraction (XRD) analysis. Precise signal assignments in NMR spectra are important in probing structural features; for this objective detailed 2D-NMR spectra were recorded and analyzed.

EXPERIMENTAL

Melting points were recorded on an electrically heated Köfler Block apparatus and are uncorrected. Column and thin layer chromatography were performed using neutral alumina and silica gel G, respectively. Spots on TLC chomatograms were visualized with iodine vapour. Analytical samples were routinely dried over anhydrous $CaCl_2$ *in vacuo* at room temperature.

UV and IR spectra were recorded in KBr discs on Hitachi UV-vis-NIR model U 3501 and Perkin-Elmer FT-IR model RX-9 spectrometers, respectively. ^1H & ^{13}C NMR spectra were recorded with Bruker Avance 300 instrument at 300 MHz and 75.5 MHz, and Bruker DRX 500 instrument at 500 MHz and 125.5 MHz. Mass spectrum was recorded with a JEOL JMS600 Mass spectrometer. Chemical shifts for NMR are reported in δ ppm, downfield from TMS; ^1H-^1H coupling constants are given in Hz. ^{13}C-NMR signal multiplicities were confirmed by DEPT spectra. DQF-COSY, HMQC and HMBC 2D NMR experiments were performed to unravel ^1H-^1H coupling information, and to assign ^1H- and ^{13}C-NMR signals in compound **5a**.

All chemicals were procured from Merck, India. Purities of starting materials were verified from comparison of their melting or boiling points with those recorded in literature as well as from their IR and ^1H NMR spectra.

Preparation of reactants: *C*-(4-chlorophenyl)-*N*-methyl nitrone was obtained by the microwave assisted procedure from 4-chlorobenzaldehyde and methyl hydroxylamine hydrochloride in the presence of excess aqueous $NaHCO_3$ [17]. The cinnamic acid anilides (**2-4**) were prepared by treatment of appropriate cinnamoyl chlorides, obtained from reaction of the corresponding with thionyl chloride with three molar proportion of aniline/*N*-methylaniline, followed by the usual workup [18]; the anilides were crystallized from ethanol/aqueous ethanol. The structural integrities of the starting materials were confirmed by IR and NMR spectra.

General procedure for cycloaddition reactions: The reactions of *C*-(4-chlorophenyl)-*N*-methyl nitrone (**1**) with a three-fold molar proportion of the dipolarophiles, *viz*. anilides of cinnamic acid (**2**-**4**), were carried out by refluxing the reactants in anhydrous toluene solution for 18-26 h under nitrogen atmosphere (**Scheme-I**). The crude reaction mixtures were concentrated under reduced pressure (rotary evaporator), the residues analyzed by 300 MHz ^1H NMR and then chromatographed over neutral alumina to isolate the products.

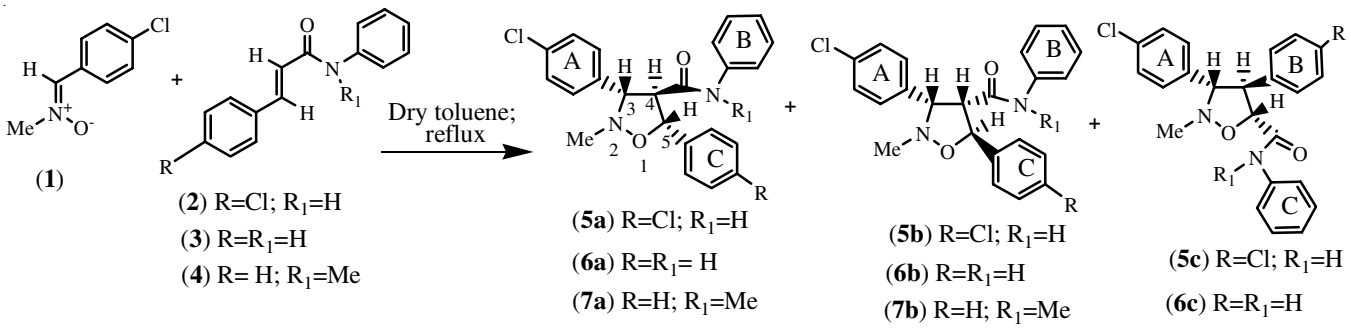
Reaction of *C*-(4-chlorophenyl)-*N*-methyl nitrone (1) (0.746 g, 0.0044 mol) with anilide of 4-chlorocinnamic acid (2) (3.400 g, 3 × 0.0044 mol). Reaction time 18 h, 300 MHz ^1H NMR analysis revealed three products formed: total conversion ~82%; ratio **5a**: **5b**: **5c** = 76:12:12. Chromatography over neutral alumina furnished compounds **5a** and **5c**.

3,4-*trans*-4,5-*trans*-2-Methyl-3,5-di(4′-chlorophenyl)-4-anilinyloxoisoxazolidine (5a): Colour: white microcrystals, m.p. 162 ºC, isolated yield 0.97 g (52%), isolated from 10% benzene in hexane eluates, R_f 0.58 (silica gel G, benzene:EtOAc 4:1). 70 eV EI-MS *m/z* M^+ 426, 425 (M-1) {peak clusters typical of the presence of two chlorines in the molecule), *m/z* 306-310 cluster (M^+-CONHPh), 257, 194, 165 [ClC_6H_4-CH=CH-CO]$^+$,152, 140 (Cl-C_6H_4-$CHO^{+\bullet}$), 139, 137, 111 ($C_6H_4Cl^+$), 77 ($C_6H_5^+$), 75 ($C_6H_3^+$), 64 ($C_5H_4^{+\bullet}$). UV (EtOH): λ_{max} 223 nm (log ε 3.55); IR (KBr, ν_{max}, cm^{-1}): 3295 (-NH-), 2875 & 2812 (CH), 1662 (amide CO), 1090 & 509 (aryl Cl), 822 (1,4-disubstituted benzene ring), 748 & 690 (mono-substituted benzene ring). Elemental analysis calcd. (found) (%) of $C_{23}H_{20}N_2O_2Cl_2$: C: 64.6 (64.3); H: 4.7 (4.5); N: 6.5 (6.3).

3,4-*trans*-4,5-*trans*-2-Methyl-3,4-di(4′-chlorophenyl)-5-anilinyloxo isoxazolidine (5c): Colourless crystals, m.p. 140-144 ºC, isolated yield 0.111g (6%), isolated from hexane eluates, R_f 0.62 (silica gel G, benzene: EtOAc = 4:1). IR (KBr, ν_{max}, cm^{-1}): 3374 (-NH-), 2937, 2874 & 2812 (CH), 1685 (amide C=O), 1094 & 508 (aryl Cl), 820 (1,4-disubstituted benzene ring), 748 & 688 (mono-substituted benzene ring). ^1H NMR (300 MHz, $CDCl_3$): δ 4.55 (d, *J* = 5.2 Hz, H3), 3.84 (dd, *J* = 9.3, 5.2 Hz, H4), 3.52 (d, *J* = 9.3 Hz, H5), 8.71 (NH), 2.69 (NCH_3), 7.09-7.23 (overlapped signals of, *A*/H-2,6,3,5; *B*/H-3,5; *C*/H-4), 7.57 (d, *J* = 7.7 Hz, *B*/H-2,6), 7.03 (d, *J* = 8.5 Hz, *C*/H-2,6), 7.29 (t, *J* = 7.7 Hz, *C*/H-3,5). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 119.8 (*C*/C-2,6), 137.1 (*A*/C-1), 134.4 (*A*/C-4), 136.0 (*B*/C-1), 135.4 (*B*/C-4), 134.5 (*C*/C-1), 124.6 (*C*/C-4), 129.0, 129.0, 129.1, 129.2, 129.3 (*A*/C-2,6,3,5; *B*/C-2,6,3,5; *C*/C-3,5). Elemental analysis calcd. (found) (%) of $C_{23}H_{20}N_2O_2Cl_2$: C: 64.6 (64.4); H: 4.7 (4.6); N: 6.5 (6.4).

Detected by ^1H NMR in crude reaction mixture. **3,4 *cis*-4,5-*trans*-2-Methyl-3,4-di(4′-chlorophenyl)-5-anilinyloxo isoxazolidine (5b)**: δ 4.03 (d, *J* = 9.8 Hz, H3), 3.42 (dd, *J* = 9.8, 5.7 Hz, H4), 5.67 (d, *J* = 5.7 Hz, H5).

Reaction of *C*-(4-chlorophenyl)-*N*-methyl nitrone (1) (0.746 g, 0.0044 mol) with cinnamic acid anilide (3) (2.940 g, 3 × 0.0044 mol). Reaction time 22 h. A 300 MHz ^1H NMR



(**1**)

(**2**) R=Cl; R_1=H
(**3**) R=R_1=H
(**4**) R= H; R_1=Me

(**5a**) R=Cl; R_1=H
(**6a**) R=R_1= H
(**7a**) R=H; R_1=Me

(**5b**) R=Cl; R_1=H
(**6b**) R=R_1=H
(**7b**) R=H; R_1=Me

(**5c**) R=Cl; R_1=H
(**6c**) R=R_1=H

Scheme-I: Reactions of *C*-(4-chlorophenyl)-*N*-methylnitrone with substituted cinnamic acid anilides

analysis revealed three products formed: total conversion ~70%; ratio **6a**: **6b**: **6c** = 70:15:15. Chromatography over neutral alumina furnished compounds **6a** and **6c**.

3,4-*trans*-4,5-*trans*-2-Methyl-3-(4′-chlorophenyl)-5-phenyl-4-anilinyloxoisoxazolidine (6a): White microcrystalline solid, m.p. 152-154 ºC, isolated yield 0.73g (42%) from 5% benzene in petroleum ether (60-80 ºC) eluates, R_f 0.46 (silica gel G, benzene). IR (KBr, ν_{max}, cm^{-1}): 3306 (NH), 3061, 2928, 2854 & 2367 (CH), 1658 (amide CO), 1091, 1021 & 506 (aryl Cl), 831 (1,4-disubstituted benzene ring), 745 & 693 (mono-substituted benzene ring). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.18 (d, *J* = 9.0Hz, H3), 3.23 (dd, *J* = 9.0, 7.5 Hz, H4), 5.53 (d, *J* = 7.5 Hz, H5), 2.78 (s, N-CH_3), 8.05 (s, NH), 7.30-7.45 (overlapped signals of *A*/H-2,6,3,5; *C*/H-2,6,3,5), 7.10-7.30 (overlapped signals of, *B*/H-2,3,4,5,6), 7.50 (d, *J* = 7.1 Hz, H-2,6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 76.4 (C3), 69.7 (C4), 81.4 (C5), 43.8 (N-CH_3), 167.2 (CO), 119.9 (*B*/C-2,6), 124.9 (*B*/C-4), 126.0 (*C*/C-2,6), 128.8, 128.9, 129.0, 129.2 (*A*/C-2,6,3,5; *B*/C-3,5; *C*/C-3,5), 129.1 (*C*/C-4), 134.2 (*A*/C-4), 137.0, 136.4 (*A*/C-1; *B*/C-1), 141.2 (*C*/C-1). Elemental analysis calcd. (found) (%) of $C_{23}H_{21}N_2O_2Cl$: C: 70.3 (70.1), H: 5.35 (5.2), N: 7.1 (6.9).

3,4-*trans*-4,5-*trans*-2-Methyl-3-(4′-chlorophenyl)-4-phenyl-5-anilinyloxoisoxazolidine (6c): Yellow low-melting solid, m.w. $C_{23}H_{21}N_2O_2Cl$, m.p. 39 ºC, isolated yield 0.12g (7%) from 5% benzene in petroleum ether (60-80 ºC) eluates along with the major compound **6a** - after recrystallisation the major compound separated out, the minor product **6c** was obtained from mother liquor. R_f 0.52 (silica gel G, benzene:EtOAc = 4:1). IR (KBr, ν_{max}, cm^{-1}): 3393 (NH), 2921& 2853 (CH), 1660 (amide CO), 1091 & 1016 & 500 (aryl Cl), 819 (1,4-disubstituted benzene ring), 755 & 696 (mono-substituted benzene ring). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.58 (d, *J* = 5.0 Hz, H3), 3.85 (dd, *J* = 9.0, 5.0 Hz, H4), 3.54 (d, *J* = 9.0 Hz, H5), 2.67 (s, N-CH_3), 8.22 (s, -NH-), 7.14-7.31 (m, ovl., *A*/H-2,6,3,5; *B*/H-3,5), 7.45 (d, *J* = 7.6 Hz, *B*/H-2,6), 7.03-7.14 (overlapped signals of, *C*/H-2,3,4,5,6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 83.3 (C-3), 81.9 (C-4), 63.2 (C-5), 170.5 (CO), 43.1(N-CH_3), 137.3 (*A*/C-1), 134.7 (*A*/C-4), 138.0 (*B*/C-1), 127.2 (*B*/C-2,6), 129.4 (*B*/C-4), 134.7 (*C*/C-1), 120.8 (*C*/C-2,6), 124.4 (*C*/C-4), 128.9, 129.0, 129.2, 129.9 (*B*/C-3,5; *C*/C-3,5; *A*/C-2,6,3,5). Elemental analysis calcd. (found) (%) of $C_{23}H_{21}N_2O_2Cl$: C: 70.3 (70.5), H: 5.35 (5.5), N: 7.1 (6.9).

Detected by ^{1}H NMR in crude reaction mixture. **3,4-*cis*-4,5-*trans*-2-Methyl-3-(4′-chlorophenyl)-5-phenyl-4-anilinyl-oxo isoxazolidine (6b)**: δ 3.92 (d, *J* = 8.9 Hz, H-3), 3.52 (dd, *J* = 8.9, 5.4 Hz, H-4), 5.61 (d, *J* = 5.4 Hz, H-5).

Reaction of *C*-(4-chlorophenyl)-*N*-methyl nitrone (1) (0.720 g, 0.0042 mol) with *N*-methylanilide of cinnamic acid (4) (2.94 g, 3 × 0.0042 mol). Reaction time 26 h, 300 MHz ^{1}H NMR analysis revealed two products formed: total conversion 62%; ratio **7a**:**7b** = 93:7. Chromatography over neutral alumina furnished (**7a**).

3,4-*trans*-4,5-*trans*-2-Methyl-3-(4′-chlorophenyl)-5-phenyl-4-(*N*-methylanilinyl)oxoisoxazolidine (7a): Yellow amorphous solid from hexane eluates after preparative TLC, R_f 0.49 (silica gel G, benzene: ethyl acetate= 4:1), (isolated yield 0.84 g, 50%). IR (KBr, ν_{max}, cm^{-1}): 3057, 3030 & 2880 (CH), 1651 (amide CO), 1119 (O=C-N), 1090, 1015 & 498 (aryl Cl), 837 (1,4-disubstituted benzene ring), 763 & 698 (mono-substituted benzene ring). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22 (d, *J* = 9.0 Hz, H3), 3.38 (t, *J* = 9.0 Hz, H4), 5.47 (d, *J* = 9.0 Hz, H5), 2.77 (s, N-CH_3), 3.14 (s, CO-N-CH_3), 7.25-7.36 (overlapped signals of, *A*/H-2,6,3,5; *B*/H-2,6; *C*/H-3,5,4), 6.91 (t, *J* = 7.5 Hz, *B*/H-2,3), 7.20 (t, *J* = 7.5 Hz, *B*/C-4), 7.45 (d, *J* = 9.0 Hz, *C*/H-2,6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 77.5 (C3), 63.4 (C4), 83.4 (C5), 44.1 (N-CH_3), 37.5 (CO-N-CH_3), 168.5 (CO), 126.4, 127.0 (*A*/C-2,6; *C*/C-2,6), 127.7, 128.3 (*B*/C-4, *C*/C-4), 128.6, 128.9, 129.0, 129.2 (*A*/ C-3,5; *B*/C-2, 6,3,5; *C*/ C-3,5), 135.1 (*A*/C-4), 139.3 (*A*/C-1), 141.5, 141.9 (*B*/C-1; *C*/ C-1). Elemental analysis calcd. (found) (%) of $C_{24}H_{23}N_2O_2Cl$: C 70.8 (70.6); H 5.7 (5.6); 6.9 (6.7).

Detected by ^{1}H-NMR in crude reaction mixture. **3,4-*cis*-4,5-*trans*-2-Methyl-3-(4′-chlorophenyl)-5-phenyl-4-(*N*-methylanilinyl)oxo isoxazolidine (7b)**: H-3 δ 4.64 (*J* = 7.5 Hz); H-4 δ 3.50 (dd, *J* = 9.0, 7.5Hz); H-5 δ 5.72 (*J* = 9.0 Hz).

X-Ray Diffraction analysis of compound 5c: Crystals of compound **5c** were obtained as elongated thin needles after recrystallization from $CHCl_3$ by slow evaporation at room temperature. They were mounted on a CCD NONIUS KAPPA system operating the Mo*K*α 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 ºC. The structures were solved by direct methods (SHELXS) and refined using isotropic, then anisotropic thermal factors (SHELXL program [19]. Hydrogens were gradually introduced in the calculations and kept riding on the bonded atom during all refinements. The final statistics of the refinements are shown in Table-1, while Figs. 1-3 were drawn using the PLATON program [20].

TABLE-1
XRD ANALYSIS OF **5c**: PARAMETERS AND REFINEMENT STATISTICS

CCDC reference No.	604787
m.f.; m.w.	$C_{23}H_{20}N_2O_2Cl_2$; 427.31
System; Space group	Monoclinic; $P2_1/n$
Cell parameters	a=28.070(1) Å; b=5.5748(3) Å; c=28.0597(1) Å α=102.100 (3)°; α=γ=90°
Z / Volume ($Å^3$)	8 / 4,293.4(4)
Radiation	Mo Kα
Nb. of measured Refl.	18,452
$\lambda_{min} - \lambda_{max}$	2.10 - 20.85°
Nb. of independent refl.	3250
Nb. of obs. refl. ($F \geq 4\sigma(I)$)	2428
completeness	99 %
Final R (obs. F)	0.1002
Final R (all data)	0.0943
Final Rw (obs. F^2)	0.2290
Final Rw (all F^2 data)	0.1912
Residual in last e-map (min-max) e-	-0.30/+0.38

The crystallographic parameters and refinement statistics of compound **5c** are given in Table-1. The numberings of structures as given in these projections are those provided in the X-ray crystallographic analysis outputs.

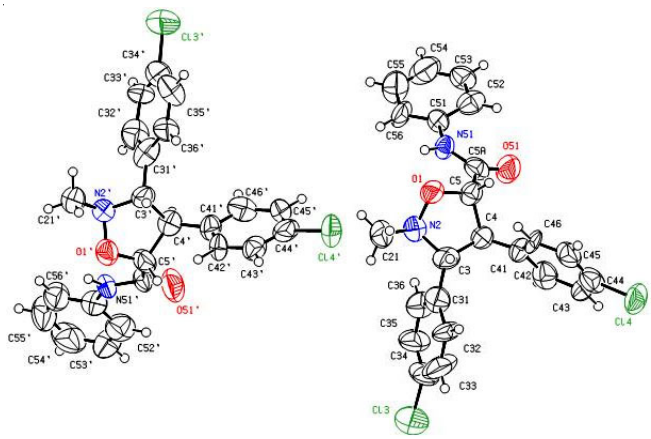


Fig. 1. XRD analysis of **5c**: ORTEP drawing of two molecules in the unit cell (ellipsoids at the 50% probability level). Hydrogen atoms are represented as small spheres with arbitrary radii

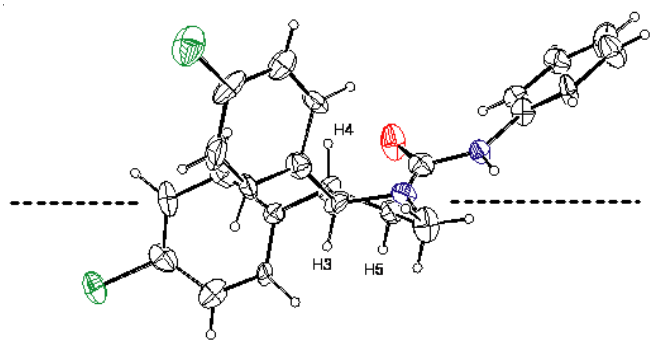


Fig. 2. XRD analysis of **5c**: view along the mean-plane of the five-membered ring (O1 is eclipsed by the N-methyl)

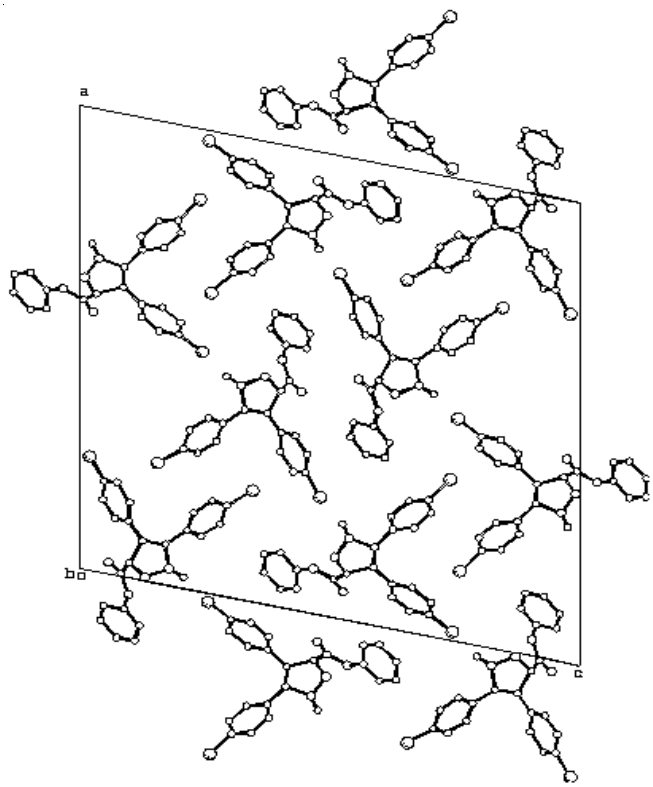


Fig. 3. XRD analysis of **5c**: Packing arrangement of the molecules in the cell (view along the b axis)

X-ray data of compound **5c** have been deposited at the Cambridge Structural Data Centre under CCDC number CCDC 604787. Parameters and refinement statistics; Positional parameters ($\times 10^4$) and mean recalculated isotropic factors ($\times 10^3$) for non-hydrogen atoms; Positional parameters ($\times 10^3$) and mean recalculated isotropic factors ($\times 10^3$) for hydrogen atoms; Anisotropic thermal parameters ($\times 10^3$) for non-hydrogen atoms; Distances (Å) for non-hydrogen atoms with e.s.d.'s given in parentheses; Bond angles (degrees) for non-hydrogen atoms with e.s.d.'s given in parentheses. 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.

RESULTS AND DISCUSSION

The [3+2] cycloadditions with *C*-(4-chlorophenyl)-*N*-methyl nitrone (**1**) are summarized in **Scheme-I**. The reactions were performed by refluxing in anhydrous toluene under nitrogen atmosphere with a threefold molar proportion of the α,β-unsaturated anilide reactants (**2**,**3**,**4**). Work-up involved removal of the solvent under reduced pressure in a rotary evaporator, followed by ^{1}H NMR analysis of the crude reaction mixture for assessing total overall yield and product ratios. The ratio of products was estimated from signal integrations in the crude mixture. The crude reaction mixtures were chromatographed over neutral alumina to isolate the products. Two diastereoisomeric 2,3,4,5-tetrasubstituted isoxazolidine cycloadducts were formed with 3,4-*trans*-4,5-*trans*-4-carboxanilido-2-methyl-3,5-diaryl isoxazolidine cycloadducts (**series a**: **5a**, **6a**, **7a**) as the major products and the diastereoisomeric 3,4-*cis*-4,5-*trans*-4-carboxanilido-2-methyl-3,5-diaryl isoxazolidine cycloadducts (series b: **5b**, **6b**, **7b**) as the minor products. In two of the reactions, the regioisomeric 3,4-*trans*-4,5-*trans*-5-carboxanilido-2-methyl-3,4-diarylisoxazolidine cycloadduct (**series c: 5c**, **6c**) were also formed as minor products. Only the major products (**5a**, **6a**, **7a**) and regioisomeric products (**5c**, **6c**) could be isolated in pure state by chromatography; the minor diastereoisomeric products (**5b**, **6b**, **7b**) were detected in the crude reaction mixtures by ^{1}H NMR analysis.

Reaction of *C*-(4-chlorophenyl)-*N*-methyl nitrone (1) with anilide of 4-chlorocinnamic acid (2): Reaction of nitrone **1** with a three-fold molar excess of anilide of 4-chlorocinnamic acid (**2**) was carried out in refluxing toluene for 18 h. ^{1}H NMR analysis of the crude reaction mixture showed the presence of three products **5a**:**5b**:**5c** in the ratio of 76:12:12, the total conversion being ~82%. Chromatography of the reaction mixture over neutral alumina furnished two isolated product **5a** and **5c**. The major cycloadduct 3,4-*trans*-4,5-*trans*-2-methyl-3,5-di(4′-chlorophenyl)-4-anilinyloxoisoxazolidine (**5a**) was purified by chromatography as a white microcrystals, m.p. 162 ºC (isolated yield 52%), from 10% benzene in hexane eluates. Compound **5c** was obtained as colourless crystals, m.p. 140-144 ºC (isolated yield 6%), from hexane eluates. Product **5b** was identified from ^{1}H NMR analysis of the crude reaction mixture.

UV spectrum of compound **5a** showed λ_{max} (EtOH) at 223 nm (log ε 3.55), indicating only the presence of non-

conjugated aromatic rings in this compound. The IR spectra (recorded in KBr disc) of compounds **5a** and **5c** showed strong absorption bands at 1662 cm^{-1} (for **5a**) and 1685 cm^{-1} (for **5c**) indicating the presence of non-conjugated amide carbonyl groups. Presence of 1,4-disubstituted benzene ring and mono substituted benzene ring was depicted by bands at 822, 748 and 690 cm^{-1} (for **5a**) and 820, 748 and 688 cm^{-1} (for **5c**), respectively. Bands at 3295 and 3374 cm^{-1} showed the presence of -NH- in the IR spectra of compounds **5a** and **5c**, respectively.

Precise signal assignments in NMR spectra are important in probing structural and stereochemical features for this objective detailed NMR studies of compound **5a** were undertaken. The structure and stereochemistry of cycloadduct **5a** were thus settled. Complete ^{1}H- & ^{13}C- signal assignments are given in Table-2; these were achieved with aid of 2D spectra 500 MHz ^{1}H-^{1}H DQF-COSY (Fig. 4); 500 MHz ^{1}H/125.5 MHz ^{13}C (HMQC) 1-bond ^{13}C-^{1}H correlation) (Fig. 5); 500 MHz ^{1}H/125.5 MHz 13C HMBC (^{13}C-^{1}H-long range correlation) (Fig. 6). The 500 MHz ^{1}H NMR spectrum ($CDCl_3$) of compound **5a** showed the isoxazolidine ring protons at δ 4.10 (d, $J_{3,4}$ = 9.0 Hz, H-3), δ 5.54 (d, $J_{4,5}$ = 7.0 Hz, H-5) and δ 3.19 (dd, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 7.0 Hz, H-4). The 500 MHz DQF-COSY of compound **5a** confirmed the coupling pattern in the isoxazolidine ring; it was particularly useful in elucidating the coupling behaviour of the aromatic protons (Fig. 4). 125.5 MHz ^{13}C NMR assignments of compound **5a** are also given in Table-2. Signal multiplicities were determined from DEPT-135° spectrum. One bond C-H couplings were determined from the HMQC spectrum (Fig. 5). The HMBC spectrum (Fig. 6) showed a long-range C-H couplings, this was particularly useful in making signal assignments, and in confirming the structure of compound **5a**. The HMBC spectrum provided the following key information regarding structure of compound **5a**: (i) C-4 showed no long-range (LR) correlations with any aromatic protons. Also *B*/C-2,6 did not show any correlations to any of the isoxazolidine protons. C-3 and C-5 both showed long-range couplings to aromatic protons; hence the two aryl rings were attached to these positions; (ii) C-5 showed LR-correlations with the doublet at δ 7.44, the *ortho*-protons (H-2,6) of the C-ring. *C*/C-2,6 showed LR-correlations to H-5; and (iii) C-3 showed LR-correlations to signal in the region δ 7.35, the *ortho*-protons (H-2,6) of the A-ring. *A*/C-2,6 showed long-range correlations to H-3.

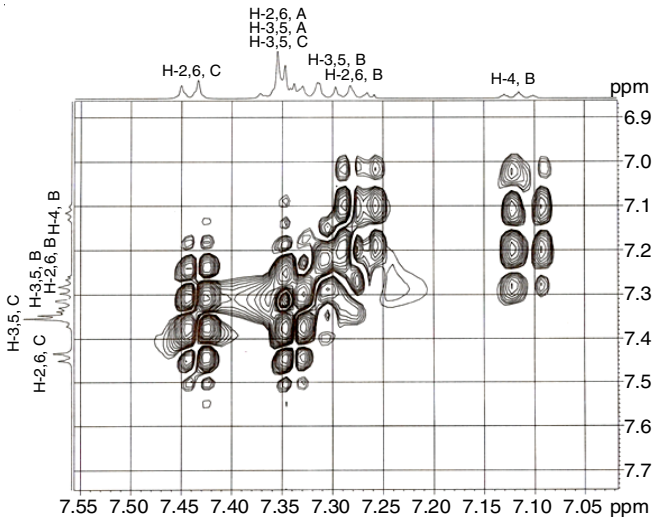


Fig. 4. 500 MHz ^{1}H-^{1}H DQF-COSY of compound **5a** in $CDCl_3$ (expansion), after D_2O exchange

The 70 eV EI mass spectrum of compound **5a** showed the molecular ion peak at *m/z* 426, the (M-1) peak appeared at *m/z* 425: both were with clusters expected of the presence of two chlorines in the molecule. Loss of the -CO-NH-Ph moiety gave cluster of peaks at *m/z* 306-310 (**Scheme-II**). These in turn generated prominent peaks at *m/z* 194 (loss of $-C_6H_4Cl$) and *m/z* 165 (loss of $ClC_6H_4CHO + H^{\bullet}$). The generation of a

TABLE-2
500 MHz ^{1}H NMR AND 125.5 MHz ^{13}C NMR ASSIGNMENTS OF **5a** IN $CDCl_3$

Proton No.	Chemical shift (δ, ppm)	Multiplicity (*J*, Hz)	Carbon No.	Chemical shift (δ, ppm)	Long range correlation with protons (from HMBC)
H-3	4.10	d, 9.0	C-3	77.2	H-4, H-5; N-CH_3; *A*/H-2,6
H-4	3.19	dd, 9.0, 7.0	C-4	70.0	H-3, H-5
H-5	5.54	d, 7.0	C-5	80.9	H-3, H-4; *C*/H-2,6
N-H	8.31	s	>CO	167.5	H-3, H-4, H-5; N-H
-N-C$\underline{H}_3$	2.75	s	-N-$\underline{C}H_3$	43.9	H-3
Ring A			*Ring A*		
H-2,6	7.32-7.38*		C-1	136.4	H-3, H-4; *A*/H-3,5
H-3,5			C-2,6	129.3#	H-3
Ring B			C-3,5	129.4#	–
H-2,6	7.25-7.32		C-4	134.9	*A*/H-2,6
H-3,5	7.11		*Ring B*		
H -4		tt, 7.2, 1.3	C-1	137.4	*B*/H-2,6, *B*/H-3,5
Ring C	7.44		C-2,6	120.4	-NH-; *B*/H-3,5, *B*/H-4,
H-2,6	7.32-7.38*	d, 8.4	C-3,5	129.5#	–
H-3,5			C-4	125.4	*B*/H-3,5, *B*/H-2,6
			Ring C		
			C-1	140.6	H-4, H-5; *C*/H-3,5
			C-2,6	127.7	H-5
			C-3,5	129.8#	–
			C-4	134.2	C/H-2,6

*Overlapped signals. #Interchangeable assignments.

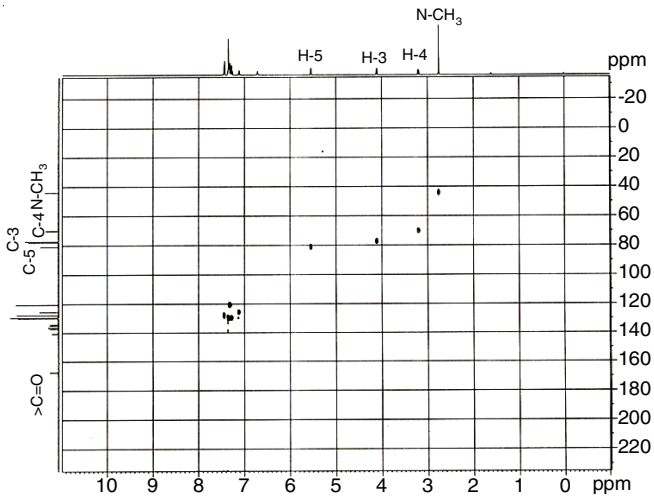


Fig. 5. 500 MHz ^{1}H NMR/125.5 MHz ^{13}C NMR heteronuclear shift correlation spectrum of compound **5a** in $CDCl_3$ using the HMQC sequence

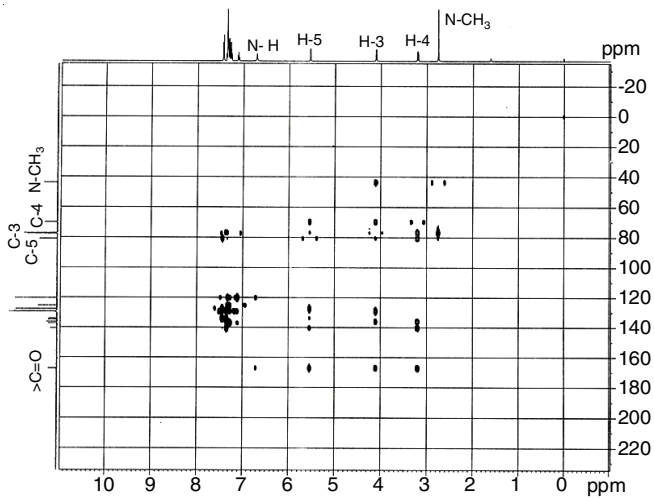
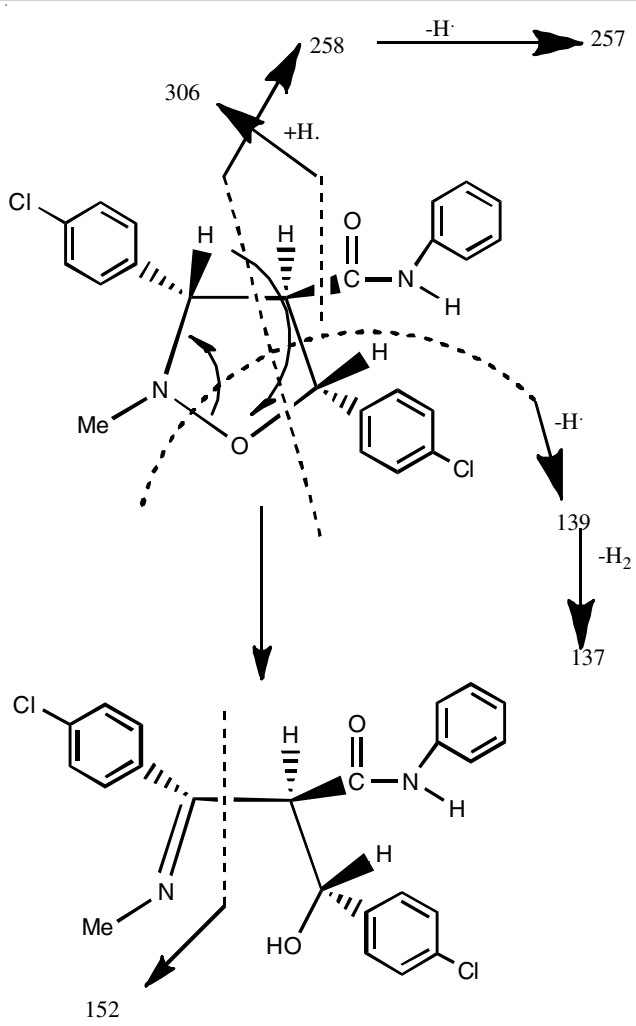


Fig. 6. 500 MHz ^{1}H NMR/125.5 MHz ^{13}C NMR heteronuclear shift correlation spectrum showing long-range couplings of compound **5a** in $CDCl_3$ using the HMBC sequence

fragment at *m/z* 257 could be explained by two alternative cleavages, corresponding to two alternative electron-impact induced cycloreversions - concomitant cleavages at 2–3 and 4–5; or cleavages at 1–5 and 3–4. The group of peaks around *m/z* 137, 139 and 140 (Cl-C_6H_4-$CHO^{+\bullet}$) correspond to concomitant cleavages at 1–2 and 4–5 with loss of hydrogen. These fragments confirmed the presence of chlorophenyl group at C-5. Rearrangement of the initially generated molecular ion followed by 3–4 cleavage gave the *m/z* 152 fragment. The fragment at *m/z* 165 corresponding to $[ClC_6H_4$-CH=CH-$CO]^+$ may be derived from simultaneous cleavage at 3–4 and 5–1.

Column chromatography over neutral alumina furnished a small amount of compound **5c** in the pure state as colourless crystals, m.p. 140-144 ºC, from the hexane eluates. Its IR absorptions were quite similar to those of cycloadduct **5a** showing the presence of same structural units. However, the ^{1}H & ^{13}C NMR spectra showed the significant differences with those of compound **5a**, particularly in the isoxazolidine part and allowed the regioisomeric structural assignment of compound **5c** to be made. Due to the interchange of aryl and carboxamido substituents at C-4 and C-5, H-4 is comparatively deshielded by ~δ 0.65 ppm and H-5 comparitively shielded by ~δ 2.0 ppm, thus there is a cross-over in the relative positions of H-4 and H-5 compared to compound **5a**. The 300 MHz ^{1}H NMR spectrum ($CDCl_3$) of compound **5c** showed the isoxazolidine ring protons δ 4.55 H-3 and δ 3.52 H-5 at and ppm respectively, appeared as doublets ($J_{4,5}$ = 9.3 Hz and $J_{3,4}$ = 5.2 Hz); the H-4 proton coupled to both of these appeared as double doublet at δ 3.52.



Scheme-II: Mass spectral fragmentation of compound **5a**

The X-ray diffraction analysis of compound **5c** was performed to confirm its structure and stereochemistry. Elongated thin needle-shaped crystals of compound **5c** were obtained after recrystallization from $CHCl_3$ by slow evaporation at room temperature. They were mounted on a CCD NONIUS KAPPA system operating the Mo*K*α radiation (λ = 0.7107 Å). Crystals were monoclinic (space group P21/n) with cell parameters a = 28.070(1) Å; b = 5.5748(3) Å; c = 28.0597(1) Å; α = 102.100(3)º; α = γ = 90º; Z / Volume (Å^3); 8 / 4,293.4(4) (Table-1). 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 ORTEP projection is shown in Fig. 1. The numberings of structures as given in these projections are those provided in the X-ray crystallographic analysis outputs. The crystal structure contains two indepen-

dent molecules in the asymmetric unit (Fig. 1), each of these being the mirror image of the other. Both molecules in each unit have nearly equivalent τ_m and P puckering parameters. The values of τ_m and P correspond to an intermediate between N2-envelope and N2-C3 twist conformations (Table-3). Looking perpendicular to the mean-plane of the five-membered ring shows that in both cases, substituents are all-*trans*, with pseudo-equatorial orientations. All angular hydrogens are pseudo-axial (Fig. 2). Packing arrangement in the cell in molecules is given in Fig. 3.

The presence of the third cycloadduct **5b**, which could not be isolated in the pure state, was detected from ^{1}H NMR analysis from the reaction mixture. The chemical shifts and coupling constants of the isoxazolidine ring protons indicated that it was diastereoisomeric with compound **5a** (Table-4) [11,12].

Reaction of *C*-(4-chlorophenyl)-*N*-methyl nitrone (1) with cinnamic acid anilide (3): Reaction of nitrone **1** with a three-fold molar excess of cinnamic acid anilide (**3**) was carried out in refluxing toluene for 22 h. 300 MHz ^{1}H NMR analysis of the crude reaction mixture revealed three products with approximate product ratio (from ^{1}H NMR integration) being **6a:6b :6c** = 70:15:15; total conversion was estimated to be ~70%. Column chromatography over neutral alumina furnished compounds **6a** and **6c** from 5% benzene in petroleum ether (60-80 ºC) eluates. 3,4-*trans*-4,5-*trans*-2-Methyl-3-(4′-chlorophenyl)-5-phenyl-4-anilinyloxoisoxazolidine (**6a**) was obtained as white solid, m.p. 152-154 ºC, (isolated yield 42%), R_f = 0.46 (silica gel G, benzene) from the 5% benzene in petroleum ether (60-80 ºC) eluates. After recrystallisation the major compound separated out and the minor product **6c** was obtained from mother liquor. Compound **6c**, R_f 0.52 (silica gel G, benzene: ethyl acetate = 4:1) was obtained as yellow low-melting solid, m.p. 39 ºC (isolated yield 7%).

The IR spectra of compounds **6a** and **6c** showed strong absorption bands at 1658 cm^{-1} (for **6a**) and 1660 cm^{-1} (for **6c**) indicating the presence of non-conjugated amide carbonyl groups. Presence of 1,4-disubstituted benzene ring and mono substituted benzene ring was depicted by 831, 745, 693 cm^{-1}, respectively (for **6a**) and 819, 755, 696 cm^{-1} (for **6c**), respectively -NH- bands appeared at 3306 cm^{-1} for **6a** and 3393 cm^{-1} for **6c**.

The 300 MHz ^{1}H NMR spectrum ($CDCl_3$) of the major product **6a** showed H-3 and H-5 at δ 4.18 and δ 5.53 ppm, respectively, appearing as doublets ($J_{3,4}$ = 9.0 Hz and $J_{4,5}$ = 7.5 Hz) H-4 appeared as double doublet at δ 3.23 ppm. An inspection of 75.5 MHz ^{13}C NMR spectra, fully decoupled and DEPT-135° of compound **6a** showed the presence of three non- aromatic methine carbons, five quaternary carbons and eight different types of aromatic CH's. The carbonyl carbon appeared at the most downfield position at δ 167.2 ppm. Assignments of the aromatic carbons of all three rings A, B and C were made on the basis of intercomparison and use of additivity parameters. The assignments based on 2D-NMR experiments for compound **5a** were particularly useful in this regard.

The IR characteristics of compound **6c** were quite similar to those of cycloadduct **6a** showing the presence of same structural units. The ^{1}H & ^{13}C NMR spectra showed significant differences with those of cycloadduct **6a**, particularly in the isoxazolidine part, and allowed the regioisomeric structural assignment of cycloadduct **6c** to be made. The relative positions of the proton signals were similar to the compounds **5a-5c** pair, the similarity in ^{1}H NMR chemical shifts and coupling constants of compound **6c** to compound **5c** allowed the structural and stereochemical assignment to be made, where H-4 was comparatively deshielded by δ 0.62 ppm and H-5 comparatively shielded by ~δ 2 ppm, with respect to cycloadduct **6a**.

The third product **6b** could not be isolated in pure state; it was identified from ^{1}H NMR of crude reaction mixture. The ^{1}H NMR characteristics of product **6b** were similar to those of product **5b**, thus allowing its stereochemical assignment to be made.

Reaction of *C*-(4-chlorophenyl)-*N*-methyl nitrone (1) with *N*-methylanilide of cinnamic acid (4): Reaction of nitrone **1** with a three-fold molar excess of *N*-methylanilide of cinnamic acid **4** was carried out in refluxing toluene for 26 h. This crude reaction mixture was concentrated in a rotary evaporator. The residue was analyzed by 300 MHz ^{1}H NMR and chromatographed over neutral alumina. ^{1}H NMR analysis of the crude reaction mixture revealed the presence of two products **7a: 7b** with approximate product ratio (from ^{1}H NMR integration) being **7a:7b** = 93:7, the total conversion being estimated to be ~62%. Chromatographic separation of the reaction mixture furnished one product **7a** from the *n*-hexane

TABLE-3
RING PUCKERING PARAMETERS IN **5c** CRYSTAL: DIHEDRAL ANGLES

Type	C3-C4	C4-C5	C5-O1	O1-N2	N2-C3	τ_m	P
1st Molecule	32.8	-6.9	-23.1	45.3	-48.8	49.4	133.4
2nd Molecule	-34.2	7.6	24.0	-46.6	50.8	51.2	133.7

TABLE-4
300 MHz ^{1}H NMR ASSIGNMENTS OF **5a**, **5b** AND **5c** IN $CDCl_3$

	5a		**5b**		**5c**	
	Chemical shift (δ, ppm)	Multiplicity (*J*, Hz)	Chemical shift (δ, ppm)	Multiplicity (*J*, Hz)	Chemical shift (δ, ppm)	Multiplicity (*J*, Hz)
H-3	4.10	d, 9.0	4.03	d, 9.8	4.55	d, 5.2
H-4	3.19	dd, 9.0, 7.0	3.42	dd, 9.8, 5.7	3.84	dd, 9.3, 5.2
H-5	5.54	d, 7.0	5.67	d, 5.7	3.52	d, 9.3

eluates. The major cycloadduct 3,4-*trans*-4,5-*trans*-2-methyl-3-(4′-chlorophenyl)-5-phenyl-4-(N-methylanilinyl)oxo isoxazolidine (**7a**), R_f 0.49 (silica gel G, benzene: ethyl acetate = 4:1), was obtained as yellow amorphous solid (isolated yield 50%) after preparative TLC,

The IR spectrum of compound **7a** showed a strong absorption band at 1651 cm^{-1} indicating the presence of non-conjugated amide carbonyl groups. Medium intensity bands at 1015, 1119 cm^{-1} indicated the presence of aryl -Cl group. Presence of 1,4-disubstituted benzene ring and monosubstituted benzene ring was depicted by bands at 837 cm^{-1} and 763, 698 cm^{-1}, respectively. Its 300 MHz ^{1}H NMR spectrum ($CDCl_3$) of compound **7a** showed that the three isoxazolidine ring protons were: H-3 and H-5 at δ 4.22 and δ 5.47 ppm, respectively appearing as doublets ($J_{3,4}$ = 9.0 Hz and $J_{4,5}$ = 9.0 Hz) and H-4 appearing as a triplet at δ 3.38 (J = 9.0 Hz). Its 75.5 MHz ^{13}C NMR spectrum showed the presence of three non-aromatic methine carbons, five quaternary carbons and eight different types of aromatic CH's as evident from the fully decoupled spectrum with DEPT-135º. The carbonyl carbon appeared at δ 168.5 ppm.

The 300 MHz ^{1}H NMR analysis of the crude reaction mixture showed that cycloadduct **7a** was overwhelmingly the major product. However weak signals identified the presence of small amounts of compound **7b**. The isoxazolidine protons for compound **7b** were observed as follows: H-3 δ 4.64 (J = 7.5 Hz); H-4 δ 3.50 (dd, J = 9.0, 7.5Hz); H-5 δ 5.72 (J = 9.0 Hz). These chemical shifts and coupling constants were similar to those of the diastereoisomeric series of cycloadducts [11,12].

Conclusions

In summary, a comparative results for four different related [3+2] cycloaddition reaction series are presented and analyzed. The results of [3+2] cycloadditions of *C*,*N*-diaryl nitrones to cinnamic acid piperidides were reported earlier (reaction series I). Subsequently, both experimental and theoretical studies on the cycloadditions of *C*-aryl-*N*-methyl nitrones to cinnamic acid piperidides (reaction series II) were also reported. This work was then extended to the [3+2] cycloadditions between *C*,*N*-diaryl nitrones to cinnamic acid anilides (reaction series III). The present investigations constitute reaction series IV. All the reactions in these four series were conducted in refluxing toluene under nitrogen atmosphere.

C,*N*-Diarylnitrones and *C*-aryl-*N*-methyl exist preferentially with the aryl rings *trans* to each other; an authorative publication has recently appeared on this aspect [21]. It is confirmed in our earlier work by ^{1}H NMR studies that the configuration of these nitrones did not change under the reaction conditions: prolonged refluxing in toluene did not give any of *cis*-diarylnitrone. Monitoring by 300 MHz ^{1}H NMR spectroscopy of the [3+2] cycloadditions showed that the relative ratios of the regio- and stereoisomeric cycloadducts remained similar as the reactions proceeded for all the series. Thus, the observed relative yields at the end of the reaction are those kinetic control (Table-5).

The major features emerged from these investigations are as follows: (i) The results were broadly similar with the major product in each reaction series was the 3,4-*trans*-4,5-*trans*-2-methyl-3,5-diaryl-4-carboxamidoisoxazolidine cycloadduct. These were obtained by *meta*, *endo*-carbonyl approach of the dipolarophile. However, there were significant differences in the degree of selectivity, and the proportions of minor products, both diastereoisomeric and regioisomeric being formed. The diastereoisomeric cycloadducts, *viz*. 3,4-*cis*-4,5-*trans*-2-methyl-3,5-diaryl-4-carboxamidoisoxazolidine derivatives were obtained in all the reaction series as minor products. These were obtained by *meta*, *exo*-carbonyl approach of the dipolarophile. The regioisomeric cycloadducts 3,4-*trans*-4,5-*trans*-3,4-diaryl-5-carboxamido isoxazolidine derivatives were obtained by *meta*, *exo*-carbonyl approach of the dipolarophile. (ii) In reaction series I, the product ratio was dependent to some extent on the electronic effect of the substituents on the nitrone and the cinnamic acid piperidides. (iii) In reaction series II, there was a significant fall in diasteroselectivity for *N*-methyl nitrones compared with *N*-phenyl nitrone; moreover the ratio was not dependent on electronic effect of the substituents on the nitrone and the cinnamic acid piperidides. An important difference was that no significant amounts of regioisomeric cycloadducts were formed. (iv) in reaction series III, the diasteroselectivity was similar to those of series I, in the cinnamic acid anilides. (v) in reaction series IV (present work) with *N*-methyl nitrone cycloadditions to cinnamic acid anilides the selectivity was less than for *N*-phenyl nitrones; comparatively larger amounts of the regioisomeric products were also formed. The diasteroselectivity was much higher for *N*-methylanilides, both in series III and IV. Also, the regioisomeric cycloadducts could not be detected for these two reactions (Table-6).

ACKNOWLEDGEMENTS

One of the authors, SSG thanks CSIR, India for a Junior Research Fellowship held at Chemistry Department, University of Calcutta, where this work was initiated; and the authorities at Department of Chemistry, Chandernagore College, Chandernagore, India for providing laboratory and computational facilities to complete this work. Another author, AB thanks University of Calcutta for providing laboratory infrastructure facilities before his retirement as Professor of Chemistry. He also thanks the Indian Science Congress Association, Depart-

TABLE-5
300 MHz ^{1}H NMR ASSIGNMENTS OF **6a**, **6b** AND **6c** IN $CDCl_3$

Proton No.	**6a**		**6b**		**6c**		Product ratio **6a:6b:6c**
	Chemical shift (δ, ppm)	Multiplicity (*J*, Hz)	Chemical shift (δ, ppm)	Multiplicity (*J*, Hz)	Chemical shift (δ, ppm)	Multiplicity (*J*, Hz)	
H-3	4.18	d, 9.0	3.92	d, 8.9	4.58	d, 4.9	
H-4	3.23	dd, 9.0, 7.5	3.52	dd, 8.9, 5.4	3.85	dd, 9.0, 4.9	70:15:15
H-5	5.53	d, 7.5	5.61	d, 5.4	3.54	d, 9.0	

TABLE-6
RATIO OF CYCLOADDUCTS IN REACTIONS WITH DIFFERENT TYPES OF *N*-SUBSTITUTED CINNAMIC ACID AMIDES

Nitrone	Alkene	Major (3,4-*trans*-4,5-*trans*)	Diastereo-isomer (3,4-*cis*-4,5-*trans*)	Regio-isomer (3,4-*trans*-4,5-*trans*)	Ref.
C,*N*-Diphenylnitrone	Cinnamic acid piperidide	92.5	7.5	–	[11,12]
C-(4-Chloro-phenyl)-*N*-phenyl nitrone	4-Chloro-cinnamic acid piperidide	81.0	10	9	[11,12]
C,*N*-Diphenylnitrone	4-Chloro-cinnamic acid piperidide	91.0	9	–	[11,12]
C-Phenyl-*N*-methyl nitrone	4-Chloro-cinnamic acid piperidide	75.0	25	–	[9]
C-(4-Chloro-phenyl)-*N*-methyl nitrone	4-Chloro-cinnamic acid piperidide	78.0	22	–	[9]
C-Phenyl-*N*-methyl nitrone	Cinnamic acid piperidide	76.0	24	–	[9]
C-(4-Chloro-phenyl)-*N*-methyl nitrone	Cinnamic acid piperidide	77.0	23	–	[9]
C-(4-Chloro-phenyl)-*N*-phenyl nitrone	4-Chloro-cinnamic acid anilide	85.0	15	–	[10]
C-(4-Chloro-phenyl)-*N*-phenyl nitrone	*N*-Methylanilide of cinnamic acid	95.0	5	–	[10]
C-(4-Chloro-phenyl)-*N*-methyl nitrone (1)	4-Chloro-cinnamic acid anilide (2)	76.0	12	12	Present work
C-(4-chloro-phenyl)-*N*-methyl nitrone (1)	Cinnamic acid anilide (3)	70.0	15	15	Present work
C-(4-Chloro-phenyl)-*N*-methyl nitrone (1)	*N*-Methylanilide of cinnamic acid (4)	93.0	7	–	Present work

ment of Science and Technology for Sir Asutosh Mookerjee Fellowship for senior scientists; and the Director-General, CCRAS, for extending the facilities of the Central Ayurveda Research Institute for Drug Development, Kolkata, India to avail this Fellowship.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. S. Sengupta and A. Banerji, *Asian J. Chem.*, **31**, 2777 (2019); https://doi.org/10.14233/ajchem.2019.22232
2. A.L. Cardoso and T.M.V.D. Pinho e Melo, *Eur. J. Org. Chem.*, 6479 (2012); https://doi.org/10.1002/ejoc.201200406
3. A.L. Cardoso and M.I.L. Soares, *Curr. Org. Chem.*, **23**, 3064 (2019); https://doi.org/10.2174/1385272823666191203122959
4. M. Baumann, I.R. Baxendale, S.V. Ley and N. Nikbin, *Beilstein J. Org. Chem.*, **7**, 442 (2011); https://doi.org/10.3762/bjoc.7.57
5. A. Padwa and W.H. Pearson, Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry towards Heterocycles and Natural Products, Chap. 1, John Wiley & Sons: New York (2002).
6. S. Nabizadeh and M. Hamzehloueian, *Theor. Chem. Acc.*, **139**, 72 (2020); https://doi.org/10.1007/s00214-020-02589-w
7. A. Banerji and P. Sengupta, *J. Indian Inst. Sci.*, **81**, 313 (2001).
8. N. Acharjee, A. Banerji and B. Gayen, *J. Indian Chem. Soc.*, **88**, 1857 (2011).
9. S. Mandal, K.K. Maiti, A. Banerji, T. Prang, A. Neuman and N. Acharjee, *Indian J. Chem.*, **57B**, 108 (2018).
10. A. Banerji, S. Sengupta, T. Prang and A. Neuman, *Indian J. Heterocycl. Chem.*, **28**, 65 (2018).
11. A. Banerji, K.K. Maiti, S. Haldar, C. Mukhopadhyay, J. Banerji, T. Prang and A. Neuman, *Monatsh. Chem.*, **131**, 901 (2000); https://doi.org/10.1007/s007060070068
12. A. Banerji, J. Banerji, S. Haldar, K.K. Maiti, S. Basu, T. Prang and A. Neuman, *Indian J. Chem.*, **37B**, 105 (1998).
13. A. Banerji, P. Sengupta, A. Neuman and T. Prang, *Indian J. Chem.*, **37B**, 15 (1998).
14. A. Banerji, D. Bandyopadhyay, P. Sengupta, B. Basak, T. Prang and A. Neuman, *Tetrahedron Lett.*, **47**, 3827 (2006); https://doi.org/10.1016/j.tetlet.2006.03.168
15. N. Acharjee, A. Banerji and T. Prang, *Monatsh. Chem.*, **141**, 1213 (2010); https://doi.org/10.1007/s00706-010-0393-2
16. N. Acharjee and A. Banerji, *Comput. Theor. Chem.*, **967**, 50 (2011); https://doi.org/10.1016/j.comptc.2011.03.040
17. A. Banerji, P.K. Biswas, P. Sengupta, S. Dasgupta and M. Gupta, *Indian J. Chem.*, **43B**, 880 (2004).
18. A.I. Vogel, A Text Book of Practical Organic Chemistry, Longmans: London, edn 4 (1978).
19. G.M. Sheldrick and T. Schneider, *Methods Enzymol.*, **277**, 319 (1997); https://doi.org/10.1016/S0076-6879(97)77018-6
20. A.L. Speck, PLATON, a Multipurpose Crystallographic tool. Utrecht University, Utrecht, The Netherlands (2001).
21. D. Roca-Lopez, T. Tejero and P. Merino, *J. Org. Chem.*, **79**, 8358 (2014); https://doi.org/10.1021/jo501698y