1,3-Dipolar Cycloaddition Reactions of 2-Substituted Azomethine *N*-Oxides with *N*-Benzyl Maleimides Leading to the Synthesis of Stereoisomers

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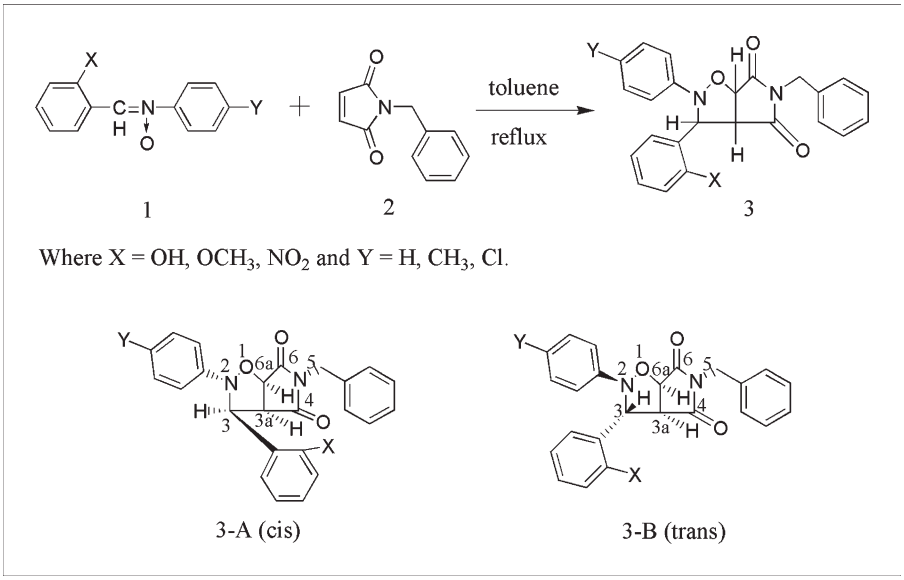

The azomethine *N*-oxides (**1**) on reacting with *N*-benzylmaleimide (**2**) provide a mixture of stereoisomers 2,3-diphenyl-5-benzyl-4*H*-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6–dione derivatives (**3**) in good yields. These isomers have been assigned cis and trans configurations (**3-A** and **3-B**) with respect to proton C_3-H on the azomethinic carbon on the basis of their PMR and H-NMR COSY data. The ratio between cis and trans isomers has been found to be dependent on substituents present at ortho position of *C*-phenyl aldehydic moiety. The salient feature of these 1,3-dipolar cycloaddition reactions lies in that the benzylic protons on *N*-benzyl moiety suffer gem coupling, indicating magnetic nonequivalence.

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INTRODUCTION

1,3-Dipolar cycloaddition reactions of azomethine *N*-oxides have been reviewed [1–4]. Present work involves the 1,3-dipolar cycloaddition reactions [5] of azomethine *N*-oxides (**1**) with *N*-benzylmaleimide (**2**) to note both the steric and electronic effect of ortho group on *C*-phenyl moiety. The required *N*-benzylmaleimide and azomethine *N*-oxides were prepared by adopting an identical procedure as reported in literature [6,7].

RESULTS AND DISCUSSION

The reaction was carried out by refluxing an equimolar of **1** and **2** in toluene to give 4*H*-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-dione derivatives [8] (**3**) (Table 1). In their IR spectra, these derivatives exhibit a strong absorption band (ν_{max}) in the range 1690–1714 cm^{-1} and a shoulder band in the range 1780–1784 cm^{-1} due to imide carbonyl groups. Usual work up of the reaction mixture provided two diastereoisomers (**3-A and 3-B**), which were characterized through their ^{1}H-NMR and ^{1}H-NMR COSY spectral data (Scheme 1).In their ^{1}H-NMR spectra, isomers showing C_3-H as singlet at δ 5.5–6.3, C_{3a}-H and C_{6a}-H as doublets at δ 3.8–4.0 with $J \approx$ 7.24 Hz, and at δ 4.9–5.3 with $J \approx$ 7.40 Hz on coupling with protons C_{6a}-H and C_{3a}-H, respectively, were assigned trans geometry (**3-B**). However, in their ^{1}H-NMR COSY spectra, C_3-H proton appears as partially resolved doublet and C_{3a}-H proton as doublet of doublet, which may be due to the dihedral angle between C_3-H and C_{3a}-H, which probably allows smaller coupling between these protons. Although the isomers showing C_3-H and C_{6a}-H signals as doublet at δ 5.4 with $J \approx$ 8.92 Hz and at δ 5.1 with $J \approx$ 7.56 Hz, respectively, and C_{3a}-H as doublet of doublet at δ 4.3 with $J \approx$ 8.88 and 7.68

Table 1

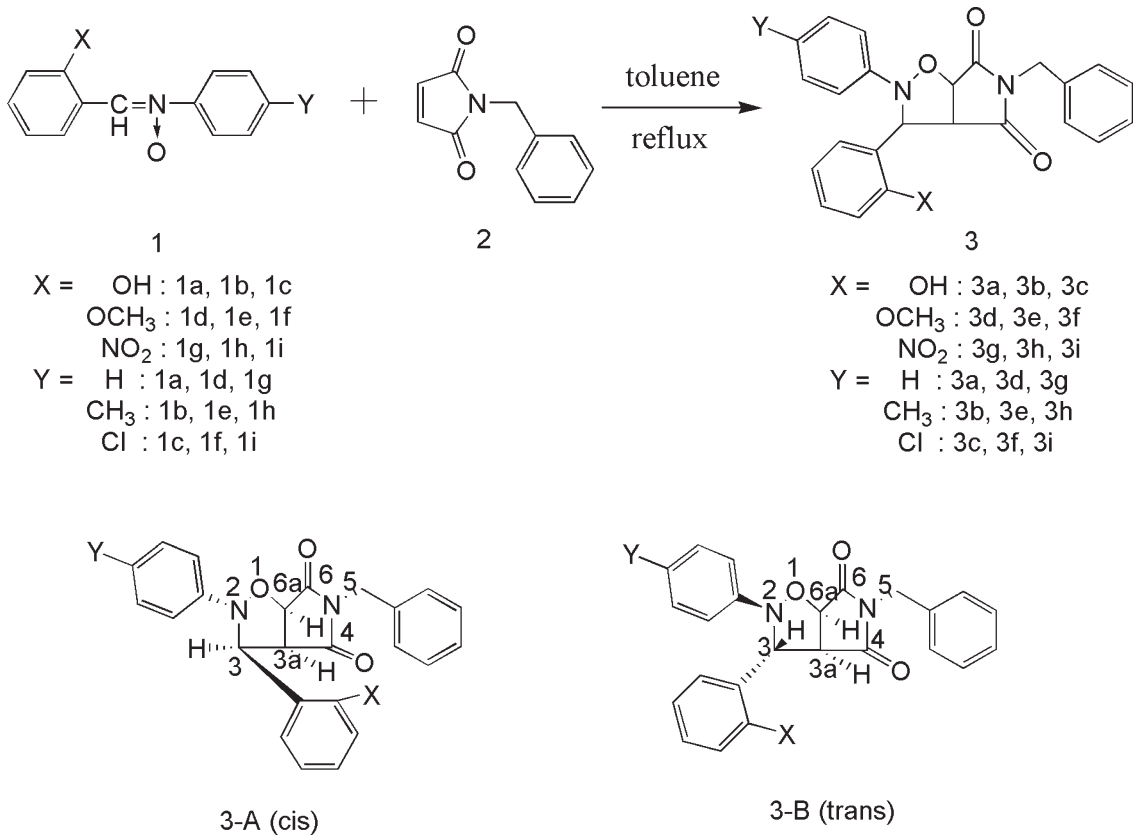
Synthesis of 2,3-diphenyl-5-benzyl-4*H*-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-dione derivatives.

			Yield (%)			Melting point (°C)	
Compounds	X	Y	A	B	A:B	A	B
3a	2-OH	4-H	61.4	12.6	83:17	205–206	138–139
3b	2-OH	4-CH_3	67.2	14.8	82:18	210–211	130–131
3c	2-OH	4-Cl	54.4	13.6	80:20	229–230	130–131
3d	2-OCH_3	4-H	10.9	67.1	14:86	185–186	132–133
3e	2-OCH_3	4-CH_3	12.6	71.4	15:85	180–181	142–143
3f	2-OCH_3	4-Cl	10.8	61.2	15:85	182–183	135–136
3g	2-NO_2	4-H	9.6	64.4	13:87	192–193	130–131
3h	2-NO_2	4-CH_3	9.4	57.6	14:86	178–179	132–133
3i	2-NO_2	4-Cl	9.9	52.1	16:84	190–191	139–140

Hz on coupling with both protons C_3-H and C_{6a}-H were assigned cis geometry [9,10] **(3-A)**.

In the case of **3a-A** (X = OH, Y = H), a one proton doublet of doublet at δ 4.3 with J = 7.64 and 8.88 Hz was assigned to C_{3a}-H, another two protons double doublet at δ 4.5 with J = 14.96 Hz was assigned to benzylic protons, a one proton doublet at δ 5.1 with J = 7.56 Hz was assigned to C_{6a}-H and another single proton doublet at δ 5.4 with J = 8.92 has been assigned to C_3-H. The aromatic protons appear as multiplets at δ 6.8–7.3 and one proton singlet at δ 9.9 was assigned to the phenolic proton, whereas in case of **3a-B**, one proton doublet at δ 3.9 with J = 7.24 Hz, two protons double doublet at δ 4.4 with J = 14.36 Hz, one proton doublet at δ 5.1 with J = 7.4 Hz and another one proton singlet at δ 5.8 have been assigned to C_{3a}-H, benzylic protons, C_{6a}-H and C_3-H, respectively. Aromatic protons integrating 14H appeared as multiplets at δ 6.8–7.3 and

Scheme 1



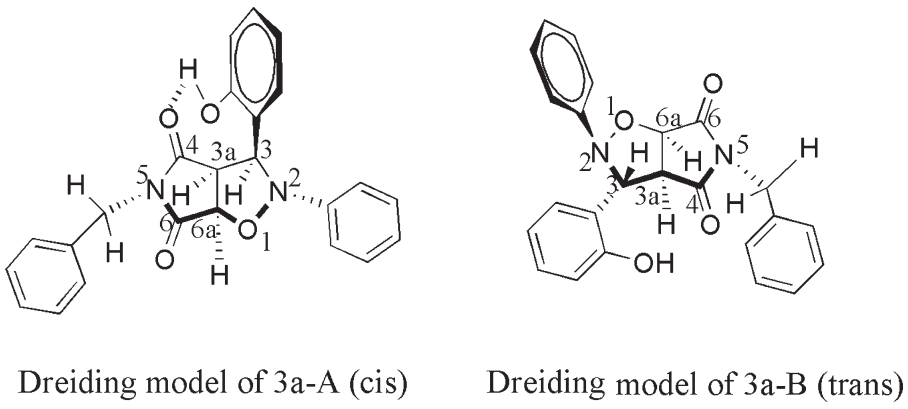


Figure 1. Dreiding models of **3a-A** (cis) and **3a-B** (trans).

single proton singlet at δ 9.5 was assigned to phenolic proton.

In these reactions, 1,3-dipole **(1)** seems to acquire thermodynamically more stable anti-configuration. With *o*-hydroxyl group on *C*-phenyl ring, the cis and trans isomeric ratio is found to be 83:17; thus, transition state of reaction seems to follow endo addition rule, and there seems to occur maximum accumulation of double bonds of the dipole-**1** as well as of the dipolarophile-**2**. The *C*-phenyl nucleus and one of the carbonyl groups of imide lie parallel during the overlap between the reacting atoms, coupled with the fact that phenolic hydrogen tends to make *H*-bond, thus, stabilizing the transition state in this form and, consequently, the dominance of cis isomer over trans isomer. The trans isomer **3-B** arises from the antiform of **1**, when the dipolarophile attacks from the other side. In this case, *N*-phenyl nucleus rather than the *C*-phenyl nucleus tends to lie nearly parallel to the double bonds of the imide carbonyl groups, which are separated by three atoms rather than two atoms as in case of previous sate. Because of the less marked effect of maximum double-bond accumulation in transition state trans isomer is formed in meagre amount (Fig. 1).

Although in cases of 2-NO_2 and 2-OCH_3 group on *C*-phenyl moiety, the cis and trans ratio is reversed, probably these substituents present at *o*-position seems to raise the energy of the transition state due to nonbonding steric interactions in the formation of cis isomer when compared with trans isomer.

It is interesting to note that the benzylic protons appear as double doublet at δ 4.2–4.6 with $J = 14.0$ Hz

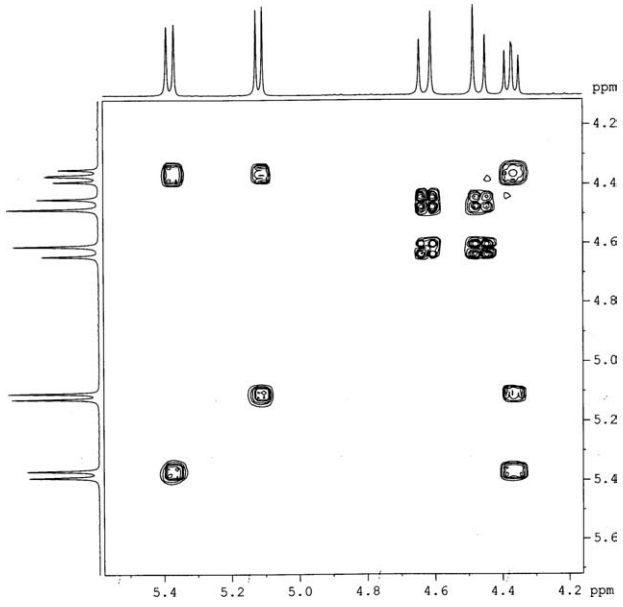


Figure 2. 400 MHz ^{1}H-NMR COSY spectrum of **3g-A** in $CDCl_3$.

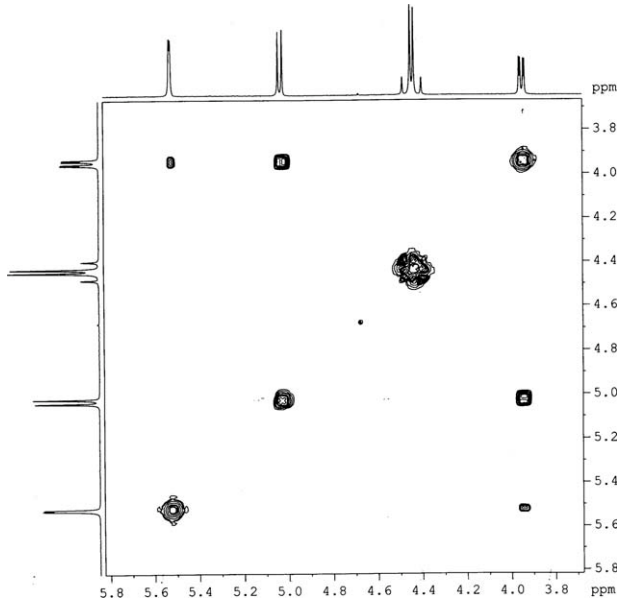


Figure 3. 400 MHz ^{1}H-NMR COSY spectrum of **3g-B** in $CDCl_3$.

revealing that these hydrogens have become magnetically nonequivalent due to nearness and deshielding effect of one of the carbonyl groups of imide moiety to one of the benzylic protons (Figs. 2 and 3).

EXPERIMENTAL

General procedures.. Melting points reported are uncorrected. IR spectra were recorded on a Perkin Elmer RXIFT infrared spectrophotometer using KBr pellets. ^{1}H-NMR and ^{1}H-NMR COSY spectra were recorded on a 400-MHz Bruker spectrometer using TMS as internal standard. Mass spectra were recorded on Waters Micromass Q-T of Micro (ESI) spectrometer. TLC plates were coated with silica gel G suspended in methanol–chloroform. Elemental analysis was carried out using Elementar vario MICRO cube CHN analyzer.

Preparation of cis-5-benzyl-3-(2-hydroxyphenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydro pyrrolo[3,4-d]isoxazole-4,6-dione (3a-A). To the aldonitrone **1a** (1.065 g, 5 mmol) were added *N*-benzyl maleimide **2** (0.935 g, 5 mmol) and toluene (25 mL), and the mixture was refluxed for 3.5 h and cooled under water tap. The crude product that separated out was recrystallized from toluene to give cis-isomer **(3a-A)** in 61.4% yield as a colorless solid, m.p. 205–206°C; ^{1}H-NMR ($CDCl_3$), δ_H 4.3 (dd, 1H, J = 7.64 and 8.88 Hz); 4.5 (dd, 2H, J = 14.96 Hz); 5.1 (d, 1H, J = 7.56 Hz); 5.4 (d, 1H, J = 8.92 Hz); 6.8–7.3 (m, 14H); 9.9 (s, 1H); IR (KBr pellets): 1690, 1781 cm^{-1} (C=O); MS: *m/z*: 400 $[M]^+$, Anal. Calcd for $C_{24}H_{20}N_2O_4$: C, 72.00; H, 5.00; N, 7.00, Found: C, 71.89; H, 5.09; N, 7.11.

Preparation of trans-5-benzyl-3-(2-hydroxyphenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydro pyrrolo[3,4-d]isoxazole-4,6-dione (3a-B). The mother liquor obtained after separation of cis-isomer upon work up gave trans-isomer **(3a-B)** as a colorless solid, which was recrystallized from toluene–ether; 12.6% yield, m.p. 138–139°C; ^{1}H-NMR ($CDCl_3$), δ_H 3.9 (d, 1H, J = 7.24 Hz); 4.4 (dd, 2H, J = 14.36 Hz); 5.1 (d, 1H, J = 7.4 Hz); 5.8 (s, 1H); 6.8–7.3 (m, 14H); 9.5 (s, 1H); IR (KBr pellets): 1690, 1781 cm^{-1} (C=O); MS: *m/z*: 400 $[M]^+$, Anal. Calcd for $C_{24}H_{20}N_2O_4$: C, 72.00; H, 5.00; N, 7.00, Found: C, 71.93; H, 5.17; N, 7.06.

Preparation of cis-5-benzyl-3-(2-hydroxyphenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydro pyrrolo[3,4-d]isoxazole-4,6-dione (3b-A). To the aldonitrone **1b** (1.135 g, 5 mmol) were added *N*-benzyl maleimide **2** (0.935 g, 5 mmol) and toluene (25 mL), and the mixture was refluxed for 3.5 h and cooled under water tap. The crude product that separated out was recrystallized from toluene to give cis-isomer **(3b-A)** in 67.2% yield as a colorless solid, m.p. 210–211°C; ^{1}H-NMR ($CDCl_3$), δ_H 2.2 (s, 3H); 4.3 (dd, 1H, J = 7.64 and 8.80 Hz); 4.5 (dd, 2H, J = 15.16 Hz);5.1 (d, 1H, J = 7.56 Hz); 5.4 (d, 1H, J = 8.92 Hz); 6.8–7.3 (m, 13H); 9.9 (s, 1H); IR (KBr pellets): 1692, 1780 cm^{-1} (C=O); MS: *m/z*: 414 $[M]^+$, Anal. Calcd for $C_{25}H_{22}N_2O_4$: C, 72.46; H, 5.31; N, 6.76, Found: C, 72.35; H, 5.11; N, 6.91.

Preparation of trans-5-benzyl-3-(2-hydroxyphenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydro pyrrolo[3,4-d]isoxazole-4,6-dione (3b-B). The mother liquor obtained after separation of cis-isomer on workup gave trans-isomer **(3b-B)** as a colorless solid, which was recrystallized from toluene–ether; 14.8% yield, m.p. 130–131°C; ^{1}H-NMR ($CDCl_3$), δ_H 2.2 (s, 3H); 4.0 (d, 1H, J = 7.36 Hz); 4.3 (dd, 2H, J = 15.08 Hz); 5.3 (d, 1H, J = 7.36 Hz); 5.7 (s, 1H); 6.8–7.3 (m, 13H); 9.5 (s, 1H); IR (KBr pellets): 1692, 1782 cm^{-1} (C=O); MS: *m/z*: 414 $[M]^+$, Anal. Calcd for $C_{25}H_{22}N_2O_4$: C, 72.46; H, 5.31; N, 6.76, Found: C, 72.52; H, 5.44; N, 6.56.

Preparation of cis-5-benzyl-3-(2-hydroxyphenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydro pyrrolo[3,4-d]isoxazole-4,6-dione (3c-A). To the aldonitrone **1c** (1.238 g, 5 mmol) were added *N*-benzyl maleimide **2** (0.935 g, 5 mmol) and toluene (25 mL), and the mixture was refluxed for 3.5 h and cooled under water tap. The crude product that separated out was recrystallized from toluene to give cis-isomer **(3c-A)** in 54.4% yield as a colorless solid, m.p. 229–230°C; ^{1}H-NMR ($CDCl_3$), δ_H 4.3 (dd, 1H, J = 7.72 and 8.80 Hz); 4.6 (dd, 2H, J = 14.92 Hz); 5.1 (d, 1H, J = 7.56 Hz); 5.4 (d, 1H, J = 8.92 Hz); 6.8–7.3 (m, 13H); 9.9 (s, 1H); IR (KBr pellets): 1691, 1782 cm^{-1} (C=O); MS: *m/z* : 434$[M]^+$, 436$[M+2]^+$, Anal. Calcd for $C_{24}H_{19}N_2O_4Cl$: C, 66.28; H, 4.37; N, 6.44, Found: C, 66.80; H, 4.25; N, 6.36.

Preparation of trans-5-benzyl-3-(2-hydroxyphenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydro pyrrolo[3,4-d]isoxazole-4,6-dione (3c-B). The mother liquor obtained after separation of cis-isomer on workup gave trans-isomer **(3c-B)** as a colorless solid, which was recrystallized from toluene–ether; 13.6% yield, m.p. 130–131°C; ^{1}H-NMR ($CDCl_3$), δ_H 4.0 (d, 1H, J = 7.48 Hz); 4.3 (dd, 2H, J = 15.0 Hz); 5.3 (d, 1H, J = 7.40 Hz); 5.7 (s, 1H); 6.8–7.3 (m, 13H); 9.4 (s, 1H); IR (KBr pellets): 1691, 1782 cm^{-1} (C=O); MS: *m/z*: 434$[M]^+$, 436$[M+2]^+$, Anal. Calcd for $C_{24}H_{19}N_2O_4Cl$: C, 66.28; H, 4.37; N, 6.44, Found: C, 65.74; H, 4.26; N, 6.27.

Preparation of cis-5-benzyl-3-(2-methoxyphenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydro pyrrolo[3,4-d]isoxazole-4,6-dione (3d-A). To the aldonitrone **1d** (1.135 g, 5 mmol) were added *N*-benzyl maleimide **2** (0.935 g, 5 mmol) and toluene (25 mL), and the mixture was refluxed for 3.0 h and cooled under water tap. The crude product that separated out was recrystallized from toluene to give cis-isomer **(3d-A)** in 10.9% yield as a colorless solid, m.p. 185–186°C; ^{1}H-NMR ($CDCl_3$), δ_H 3.9 (s, 3H, OCH_3); 4.3 (dd, 1H, J = 7.68 and 8.76 Hz); 4.5 (dd, 2H, J = 13.84 Hz); 5.1 (d, 1H, J = 7.56 Hz); 5.4 (d, 1H, J = 8.92 Hz), 6.7–7.3 (m, 14H); IR (KBr pellets): 1715, 1783 cm^{-1} (C=O); MS: *m/z* : 414 $[M]^+$, Anal. Calcd for $C_{25}H_{22}N_2O_4$: C, 72.46; H, 5.32; N, 6.76, Found: C, 72.55; H, 5.12; N, 6.57.

Preparation of trans-5-benzyl-3-(2-methoxyphenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydro pyrrolo[3,4-d]isoxazole-4,6-dione (3d-B). The mother liquor obtained after separation of cis-isomer on workup gave trans-isomer **(3d-B)** as a colorless solid, which was recrystallized from toluene–ether; 67.1% yield, m.p. 132–133°C; ^{1}H-NMR ($CDCl_3$), δ_H 3.5 (s, 3H, OCH_3); 3.8 (d, 1H, J = 7.32 Hz); 4.2 (dd, 2H, J = 14.0 Hz); 4.9 (d, 1H, J = 7.40 Hz); 6.3 (s, 1H); 6.8–7.3 (m, 14H); IR (KBr pellets): 1715, 1783 cm^{-1} (C=O); MS: *m/z*: 414 $[M]^+$, Anal. Calcd for $C_{25}H_{22}N_2O_4$: C, 72.46; H, 5.32; N, 6.76, Found: C, 72.20; H, 5.27; N, 6.82.

Preparation of cis-5-benzyl-3-(2-methoxyphenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydro pyrrolo[3,4-d]isoxazole-4,6-dione (3e-A). To the aldonitrone **1e** (1.205 g, 5 mmol) were added *N*-benzyl maleimide **2** (0.935 g, 5 mmol) and toluene (25 mL), and the mixture was refluxed for 3.0 h and cooled under water tap. The crude product that separated out was recrystallized from toluene to give cis-isomer **(3e-A)** in 12.6% yield as a colorless solid, m.p. 180–181°C; ^{1}H-NMR ($CDCl_3$), δ_H 2.2 (s,

3H); 3.9 (s, 3H, OCH_3); 4.3 (dd, 1H, J = 7.64 and 8.88 Hz); 4.5 (dd, 2H, J = 14.8 Hz), 5.1 (d, 1H, J = 7.56 Hz); 5.4 (d, 1H, J = 8.92 Hz), 6.7–7.3 (m, 13H); IR (KBr pellets): 1714, 1783cm^{-1} (C=O); MS: *m/z* : 428 $[M]^+$, Anal. Calcd for $C_{26}H_{24}N_2O_4$: C, 72.90; H, 5.61; N, 6.54, Found: C, 72.70; H, 5.47; N, 6.68.

Preparation of trans-5-benzyl-3-(2-methoxyphenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydro pyrrolo[3,4-d]isoxazole-4,6-dione (3e-B). The mother liquor obtained after separation of cis-isomer on workup gave trans-isomer **(3e-B)** as a colorless solid, which was recrystallized from toluene–ether; 71.4% yield, m.p. 142–143°C; ^{1}H-NMR ($CDCl_3$), δ_H 2.2 (s, 3H); 3.5 (s, 3H, OCH_3); 3.8 (d, 1H, J = 7.36 Hz); 4.2 (dd, 2H, J = 13.9 Hz); 4.9 (d, 1H, J = 7.40 Hz); 6.3 (s, 1H); 6.8–7.3 (m, 13H); IR (KBr pellets): 1714, 1783 cm^{-1} (C=O); MS: *m/z*: 428 $[M]^+$, Anal. Calcd for $C_{26}H_{24}N_2O_4$: C, 72.90; H, 5.61; N, 6.54, Found: C, 72.41; H, 5.73; N, 6.78.

Preparation of cis-5-benzyl-3-(2-methoxyphenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydro pyrrolo[3,4-d]isoxazole-4,6-dione (3f-A). To the aldonitrone **1f** (1.308 g, 5 mmol) were added *N*-benzyl maleimide **2** (0.935 g, 5 mmol) and toluene (25 mL), and the mixture was refluxed for 3.0 h and cooled under water tap. The crude product that separated out was recrystallized from toluene to give cis-isomer **(3f-A)** in 10.8% yield as a colorless solid, m.p. 182–183°C; ^{1}H-NMR ($CDCl_3$), δ_H 3.8 (s, 3H, OCH_3); 4.3 (dd, 1H, J = 7.72 and 8.92 Hz); 4.5 (dd, 2H, J = 14.8 Hz), 5.1 (d, 1H, J = 7.56 Hz); 5.4 (d, 1H, J = 8.92 Hz), 6.7–7.3 (m, 13H); IR (KBr pellets): 1714, 1784 cm^{-1} (C=O); MS: *m/z*: 448$[M]^+$, 450$[M+2]^+$, Anal. Calcd for $C_{25}H_{21}N_2O_4Cl$: C, 66.89; H, 4.68; N, 6.24, Found: C, 66.49; H, 4.81; N, 6.25.

Preparation of trans-5-benzyl-3-(2-methoxyphenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydro pyrrolo[3,4-d]isoxazole-4,6-dione (3f-B). The mother liquor obtained after separation of cis-isomer on workup gave trans-isomer **(3f-B)** as a colorless solid, which was recrystallized from toluene–ether; 61.2% yield; m.p. 135–136°C; ^{1}H-NMR ($CDCl_3$), δ_H 3.5 (s, 3H, OCH_3); 4.0 (d, 1H, J = 7.52 Hz); 4.3 (dd, 2H, J = 13.82 Hz); 5.3 (d, 1H, J = 7.36 Hz); 5.7 (s, 1H); 6.8–7.3 (m, 13H); IR (KBr pellets): 1714, 1784 cm^{-1} (C=O); MS: *m/z*: 448$[M]^+$, 450$[M+2]^+$, Anal. Calcd for $C_{25}H_{21}N_2O_4Cl$: C, 66.89; H, 4.68; N, 6.24, Found: C, 66.34; H, 4.82; N, 6.07.

Preparation of cis-5-benzyl-3-(2-nitrophenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydropyrrolo [3,4-d]isoxazole-4,6-dione (3g-A). To the aldonitrone **1g** (1.210 g, 5 mmol) were added *N*-benzyl maleimide **2** (0.935 g, 5 mmol) and toluene (25 mL), and the mixture was refluxed for 4 h and cooled under water tap. The crude product that separated out was recrystallized from toluene to give cis-isomer **(3g-A)** in 9.6% yield as a colorless solid, m.p. 192–193°C; ^{1}H-NMR ($CDCl_3$), δ_H 4.3 (dd, 1H, J = 7.72 and 8.88 Hz); 4.5 (dd, 2H, J = 13.8 Hz); 5.1 (d, 1H, J = 7.56 Hz); 5.4 (d, 1H, J = 8.92 Hz); 6.8–7.3 (m, 14H); IR (KBr pellets): 1714, 1782 cm^{-1} (C=O); MS: *m/z*: 429 $[M]^+$, Anal. Calcd for $C_{24}H_{19}N_3O_5$: C, 67.13; H, 4.43; N, 9.79, Found: C, 66.51; H, 4.34; N, 10.12.

Preparation of trans-5-benzyl-3-(2-nitrophenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydro pyrrolo[3,4-d]isoxazole-4,6-dione (3g-B). The mother liquor obtained after separation of cis-isomer on workup gave trans-isomer **(3g-B)** as a colorless solid, which was recrystallized from toluene–ether; 64.4% yield, m.p. 130–131°C; ^{1}H-NMR ($CDCl_3$), δ_H 3.9 (d, 1H, J = 7.36 Hz); 4.4 (dd, 2H, J = 14.0 Hz); 5.0 (d, 1H, J = 7.36 Hz); 5.5 (s, 1H); 6.8–7.3 (m, 14H); IR (KBr pellets):1714, 1782 cm^{-1} (C=O); MS: *m/z* (%): 429 $[M]^+$, Anal. Calcd for $C_{24}H_{19}N_3O_5$: C, 67.13; H, 4.43; N, 9.79, Found: C, 67.31; H, 4.48; N, 10.08.

Preparation of cis-5-benzyl-3-(2-nitrophenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydropyrrolo [3,4-d]isoxazole-4,6-dione (3h-A). To the aldonitrone **1h** (1.280 g, 5 mmol) were added *N*-benzyl maleimide **2** (0.935 g, 5 mmol) and toluene (25 mL), and the mixture was refluxed for 4 h and cooled under water tap. The crude product that separated out was recrystallized from toluene to give cis-isomer **(3h-A)** in 9.4% yield as a colorless solid, m.p. 178–179°C; ^{1}H-NMR ($CDCl_3$), δ_H 2.2 (s, 3H); 4.3 (dd, 1H, J = 7.64 and 8.84 Hz); 4.6 (dd, 2H, J = 15.12 Hz); 5.1 (d, 1H, J = 7.56 Hz); 5.4 (d, 1H, J = 8.92 Hz); 6.8–7.3 (m, 13H); IR (KBr pellets): 1714, 1785 cm^{-1} (C=O); MS: *m/z*: 443 $[M]^+$, Anal. Calcd for $C_{25}H_{21}N_3O_5$: C, 67.72; H, 4.74; N, 9.48, Found: C, 67.36; H, 4.81; N, 9.18.

Preparation of trans-5-benzyl-3-(2-nitrophenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydro pyrrolo[3,4-d]isoxazole-4,6-dione (3h-B). The mother liquor obtained after separation of cis-isomer on workup gave trans-isomer **(3h-B)** as a colorless solid, which was recrystallized from toluene–ether; 57.6% yield, m.p. 132–133°C; ^{1}H-NMR ($CDCl_3$), δ_H 2.2 (s, 3H); 3.8 (d, 1H, J = 7.48 Hz); 4.2 (dd, 2H, J = 15.10 Hz); 4.9 (d, 1H, J = 7.40 Hz); 6.3 (s, 1H); 6.8–7.3 (m, 13H); IR (KBr pellets): 1714, 1785 cm^{-1} (C=O); MS: *m/z*: 443 $[M]^+$, Anal. Calcd for $C_{25}H_{21}N_3O_5$: C, 67.72; H, 4.74; N, 9.48, Found: C, 67.27; H, 4.68; N, 9.73.

Preparation of cis-5-benzyl-3-(2-nitrophenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydropyrrolo [3,4-d]isoxazole-4,6-dione (3i-A). To the aldonitrone **1i** (1.382 g, 5 mmol) were added *N*-benzyl maleimide **2** (0.935 g, 5 mmol) and toluene (25 mL), and the mixture was refluxed for 4 h and cooled under water tap. The crude product that separated out was recrystallized from toluene to give cis-isomer **(3i-A)** in 9.9% yield as a colorless solid, m.p. 190–191°C; ^{1}H-NMR ($CDCl_3$), δ_H 4.3 (dd, 1H, J = 7.68 and 8.88 Hz); 4.5 (dd, 2H, J = 14.0 Hz); 5.1 (d, 1H, J = 7.56 Hz); 5.4 (d, 1H, J = 8.92 Hz); 6.8–7.3 (m, 13H); IR (KBr pellets): 1691, 1782 cm^{-1} (C=O); MS: *m/z*: 463$[M]^+$,465$[M+2]^+$, Anal. Calcd for $C_{24}H_{18}N_3O_5Cl$: C, 62.14; H, 3.88; N, 9.06, Found: C, 62.51; H, 3.79; N, 8.73.

Preparation of trans-5-benzyl-3-(2-nitrophenyl)-2-phenyl-4H-2,3,3a,5,6,6a-hexahydro pyrrolo[3,4-d]isoxazole-4,6-dione (3i-B). The mother liquor obtained after separation of cis-isomer on workup gave trans-isomer **(3i-B)** as a colorless solid, which was recrystallized from toluene–ether; 52.1% yield; m.p. 139–140°C; ^{1}H-NMR ($CDCl_3$), δ_H 3.8 (d, 1H, J = 7.40 Hz); 4.2 (dd, 2H, J = 13.98 Hz); 4.9 (d, 1H, J = 7.36 Hz); 6.3 (s, 1H); 6.8–7.3 (m, 13H); IR (KBr pellets): 1691, 1782 cm^{-1} (C=O); MS: *m/z*: 463$[M]^+$,465$[M+2]^+$, Anal. Calcd for $C_{24}H_{18}N_3O_5Cl$: C, 62.14; H, 3.88; N, 9.06, Found: C, 62.43; H, 3.92; N, 8.75.

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