‘Huisgen reaction’ of aldonitrones with N-benzyl maleimide leading to synthesis of 2, 3-diaryl-5-benzyl-2H-3, 3a, 4, 5, 6, 6a-hexahydropyrrolo[3, 4-d]isoxazole-4, 6-diones

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1,3-Dipolar cycloaddition reaction of variously substituted aldonitrones with N-benzyl maleimide leads to the synthesis of substituted 2, 3-diaryl-5-benzyl-2H-3, 3a, 4, 5, 6, 6a-hexahydropyrrolo[3, 4-d] isoxazole-4, 6-diones in good yield. Structures and stereochemistry of the products have been determined by detailed spectral studies.

Keywords: Huisgen reaction, aldonitrones, N-benzyl maleimide, isoxazole diones, stereochemistry

IPC: Int.Cl. 7 C 07 D

1, 3-Dipolar cycloaddition reaction provides an excellent method for the synthesis of heterocyclic compounds in good yields1-3. Among the plethora of 1, 3-dipoles, nitrones have earned an important place in organic chemistry. The ‘Huisgen reaction’ of nitrones with olefins has been extensively carried out to obtain isoxazolidines4. The cycloaddition reactions of nitrones with various activated double bonds like maleimides5,6, cinnamoyl piperidines7,8 etc. and catalysed with various metals and chiral lewis acids have been reported10-12. We report herein our studies on 1, 3-dipolar cycloaddition reactions involving N-benzyl maleimide as the dipolarophile with different aldonitrones. The whole series of reactions gives a detailed study of effect of various substituents on the cycloadditions especially, when phenyl ring moves one atom away from nitrogen atom of imide moiety. For this purpose variously substituted nitrones have been prepared by using variously substituted aldehydes and variously substituted N-hydroxylamines13,14.

The cycloaddition reactions of variously substituted nitrones 1 with N-benzyl maleimide 2 have been carried out by refluxing equimolar amounts of both in sodium dried benzene (Ranbaxy). Work-up of the reaction mixture provided the crude product 3 as a single stereoisomer in good yield, which has been recrystallised from hexane-ethyl acetate (3: 1) mixture (Scheme I).

The cycloadducts 3 have been characterised as cis-2, 3-diaryl-5-benzyl-2H-3, 3a, 4, 5, 6, 6a-hexahydropyrrolo[3, 4-d]isoxazole-4, 6-diones on the basis of their melting points, elemental analysis and spectral (IR, 1H NMR and mass) data. The physical data for the products 3 are reported in Table I.

The IR spectra of 3 display two absorption bands, one is weak to medium in the region 1783-1742 cm⁻¹ and other is strong in the region 1740-1700 cm⁻¹ which have been assigned to the carbonyl stretching vibrations of imide moiety. The absorption bands in
the region 1610-1600 cm\(^{-1}\) are due to skeletal vibrations of aromatic rings and in the region 1280-1150 cm\(^{-1}\) have been assigned to nitrogen-oxygen (N-O) stretchings. Absorption band in the region 1485-1350 cm\(^{-1}\) is of CH\(_2\) bending vibrations of benzyl group. A sharp and medium absorption band in the region 1393-1376 cm\(^{-1}\), a weak absorption band at 1372-1349 cm\(^{-1}\) and two weak absorption bands at 1183-1145 and 1094-1086 cm\(^{-1}\) have been assigned to carbon-nitrogen (C-N) stretchings.

In the \(^1\)H NMR spectra of cis-2-phenyl-3-(3′-methoxy-4′-hydroxyphenyl)-5-benzyl-2H-3, 3a, 4, 5, 6, 6a-hexahydropyrrolo[3, 4-d]isoxazole-4, 6-diones 3a show a multiplet signal at \(\delta 7.35-6.57\) (equivalent to 13H, Ar-H), a singlet at \(\delta 5.5\) (1H, OH), doublet at

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δ 5.1 (1H, H₃) due to coupling with proton H₃a having coupling constant $J_{H₃-H₃a} = 7.89$ Hz. Another doublet at δ 5.07 (1H, H₃) due to coupling with proton H₃a having coupling constant $J_{H₃-H₃a} = 8.84$ Hz. A singlet at δ 4.57 (2H, -CH₂-) has been assigned to methylene protons of benzyl moiety. ¹H NMR spectra also show a triplet at δ 3.82 (1H, H₃a) due to coupling with H₃ and H₆a having coupling constants $J_{H₃-H₆a} = 8.465$Hz and $J_{H₃a-H₃} = 8.469$Hz respectively. A singlet at δ 3.6 (3H, -OCH₃) has been assigned to methoxy group.

The proton H₃ shows a downfield chemical shift as compared to protons H₆a and H₃a, because of presence of an electronegative nitrogen atom and aromatic ring adjacent to the carbon to which it is attached. The coupling constants of three protons H₃, H₃a, H₆a are approximately equal (7.9-8.8 Hz) and is a typical of vicinally coupled cis protons. Therefore the three protons of isoxazolidinone ring are in cis-orientation with one another. From the NOESY – 2D experiment of this compound (Figure 1), it is clear that H₃, H₃a and H₆a show coupling with each other and are in cis-orientation with each other.

The mass spectrum (70 eV) of 3a shows the presence of molecular ion peak as the base peak at m/z 430(100). The major fragmentation of the molecular ion occurs through the retrocycloaddition leading to peaks at m/z 243(13.6) and at m/z 187(17.1) of C-(3-methoxy-4-hydroxy)-N-phenylazomethine-N-oxide and N-benzyl maleimide, respectively. On further fragmentation it gives m/z at 242(8.9), 227(25.7), 226(26.8), 211(6.2), 104(14.0), 151(9.7), 92(6.6), 91(66.9), 77(29.6). The probable mode of fragmentation is given in Chart I.

In these dipolar cycloaddition reactions, only single stereoisomer corresponding to cis-configuration has been obtained revealing the stereochemistry of the reaction.

At the transition state the preferred approach of dipole and dipolarophile is the one where the π-π bonding and steric interactions are minimum between them. It seems that during these 1, 3-dipolar cycloadditions, in the transition state nitrone has the trans-orientation where the non-bonded steric interactions are minimum and secondary orbital interactions become dominant.

Therefore, Naryl ring of nitrone and N-benzyl ring of maleimide become almost parallel to each other in final product. Thus “anti” orientation of nitrone formed predominantly and results in formation of cis-isomer as

![Figure 1 — 300 MHz NOESY-2D spectrum of 3a in CDCl₃](image-url)
single product, because more secondary stabilisation and least bonding steric interaction occur in this form.

**Experimental Section**

Melting points were determined by open-capillary method in paraffin bath and are uncorrected. IR spectra were recorded in nujol on a Perkin-Elmer spectrum RX-I series FTIR spectrophotometer; and 

$^1$H NMR spectra on a Bruker AC-300F (300MHz) spectrometer using TMS as internal standard (chemical shifts in $\delta$, ppm). The mass spectra were recorded on VG-70-S mass spectrometer by SAIF,
Punjab University, Chandigarh. NOESY experiment have been got recorded from CIL, NIPER, Mohali.

**Synthesis of N-benzyl maleimide 2.** To the solution of maleic anhydride (0.2 mole, 19.6 g) in 75 mL dry chloroform, a solution of benzyl amine (21.4 g, 0.2 mole) in 20 mL of dry chloroform was added slowly, while stirring. The resulting thick paste was filtered to get a white powder of maleanilic acid. To this maleanilic acid was added acetic anhydride (67 ml) and anhydrous sodium acetate (6.5 g) and refluxed for 1 hr. The work-up of reaction mixture provided N-benzyl maleimide in 75% yield. It was recrystallised from pet. ether to get needle like crystals, m.p. 85-88°C (Found: C, 69.08; H, 4.69; N, 8.78. C₁₁H₉O₂N requires C, 70.58; H, 4.812; N, 7.48%).

IR (Nujol): 2946.7-2093.8, 1813.7, 1717.5, 1458.2, 1377.8, 722.8, 696.1, 452.4 cm⁻¹; ¹H NMR (300 MHz): δ 7.25 (m, 5H, Ar-H), 6.7 (d, 2H, -CH=CH-), 4.6 (s, 2H, -CH₂-).

**Synthesis of 2-phenyl-3-(3′-methoxy-4′-hydroxy-phenyl)-5-benzyl-2H-3,3a,4,5,6,6a-hexahydropyrrolo[3,4-d]isoxazole-4,6-dione 3a.** In a 250 mL round-bottomed flask fitted with a reflux condenser, a mixture of C-(3-methoxy-4-hydroxyphenyl)-N-phenylazomethine N-oxide (2.43 g, 0.01 mole) and N-benzyl maleimide (1.87 g, 0.01 mole) in sodium dried benzene (Ranbaxy) (50 mL) was heated to reflux for 12-18 hr and then cooled under the tap. The crude product that separated out, was filtered and recrystallised from hexane-ethyl acetate (3:1) mixture to get white amorphous powder, m.p. 198-200°C (Found: C, 69.56; H, 5.11; N, 6.51. C₂₅H₂₂N₂O₅ requires C, 69.01; H, 5.01; N, 8.95%); IR (Nujol): 3289.2, 2949.5, 2936.2, 1708.8, 1598.5, 1515.3, 1491.9, 1463.7, 1377.8, 1340.1, 1263, 1093.7, 1036.0, 730.0, 693.7, 465.7 cm⁻¹; ¹H NMR (300MHz): δ 6.57-7.35(13H, Ar-H), 5.5 (s, 1H, OH), 5.07 (d, 1H, H-6a, J_H1-H3a= 7.95Hz), 4.66 (d, 1H, H₃, J_H1-H₃a=8.84 Hz), 4.57 (s, 2H, -CH₂-), 3.82 (t, 1H, H₃a, J_H3a-H₃=8.46 Hz and J_H3a-H₁= 8.277 Hz), 3.6 (s, 3H, -OCH₃); MS m/z (Relative Intensity): M⁺ 430 (100), other prominent ions are at m/z 243 (13.6), 227 (25.7), 226 (26.8), 187 (17.1), 104 (14.0), 77 (29.6).

Compounds 3b-3r were prepared similarly and their physical data are given in Table I.

**Acknowledgement**

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**References**