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Non-catalytic regioselective synthesis of *trans* bis-pyrrolo isoxazole cycloadducts in water†

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Pyrrolo isoxazoles are key structural motifs of many drugs and pharmacologically active compounds and are often synthesized by one-pot cycloaddition reactions under thermal conditions. In the present study, a series of new symmetric bis-pyrrolo isoxazole cycloadducts have been synthesized by cycloaddition of bis-nitrones of glyoxal with N-substituted maleimides in water under non-catalytic conditions. The thermal cycloaddition reactions conducted in an aqueous medium at 70 °C afforded a single regioisomer of symmetric bis-pyrrolo isoxazoles in a shorter reaction period of 10–15 minutes. The formation of only the *trans* diastereoisomer, as confirmed by ^{1}H-NMR spectral analysis, was attributed to the involvement of *endo*-transition mode, where a succinimide moiety and *N*-phenyl ring of the nitrone being on the same side stabilized the transition state by maximum π–π overlap. Several pyrrolo isoxazole derivatives have been synthesized using this methodology. The present approach for pyrrolo isoxazole synthesis, being one-pot, facile, non-catalytic, and conducted at low temperature and under aqueous conditions, can be counted as a step towards sustainable and green synthetic chemistry.

Sustainability spotlight

In our continuous efforts to develop green and sustainable methods for synthesis of heterocyclic compounds of pharmacological importance, in this paper, we report the novel diastereoselective synthesis of bis-pyrrolo isoxazoles *via* 1,3-dipolar cycloadditions of glyoxal bis-nitrones with N-substituted maleimides in water. This study is significant because of the formation of a single regio-isomer (*trans* isomer) exclusively, in very short reaction times (10–15 minutes). Moreover, the binitrone and cycloaddition reactions have been performed in water. Thus, this protocol of synthesis of bis cyclo-adducts of pyrrolo isoxazoles is facile, efficient, selective and eco-friendly.

1. Introduction

The isoxazoles are crucial five-membered heterocycles with nitrogen and oxygen atoms at adjacent positions. They are an appealing target in organic, bioorganic, and pharmaceutical chemistry, and building blocks of a diverse array of pharmaceutically important compounds. They have been shown to exhibit a wide range of biological properties including antifungal,[1] antimicrobial,[2] antiviral,[3] antimycobacterial,[4] antioxidant,[5] anticonvulsant,[6] and antitumor.[7] They have also been found to have an inhibition towards HDAC,[8] protein-tyrosine phosphatase,[9] and COX-2 isozyme.[10] They are nematicidal[11] and have been used to treat leishmaniasis[12] and arthritis.[13]

While there exist several additional techniques for synthesizing oxazoles and isoxazoles, a multicomponent reaction among β-ketoesters, hydroxylamine hydrochloride, and aromatic aldehydes produces the product in higher yields in a single step. Several acidic and basic catalysts including boric acid,[14] potassium hydrogen phthalate,[15] DABCO,[16] metal-oxide nanoparticles,[17] pyridine,[18,19] and citrazinic acid[20] have been reported to catalyze the process.

Pyrrolo oxazoles and isoxazoles are an important class of pharmaceutical compounds that have been established as antimitotic,[21] antibacterial,[22] anti-stress,[23] anti-inflammatory,[24] anti-tubercular,[25] and anti-cancer agents.[26] In pyrrolo isoxazoles, a pyrrole ring is joined to an isoxazole moiety. The pyrrolo isoxazoles are often synthesized by one-pot cycloadditions of nitrones with various maleimide substrates.[27] The advantages of synthesizing them *via* the cycloaddition mode lies in that the regioselectivity of the reaction can be controlled to obtain either of the regioisomers as the product.[27,28] But in few

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cases the regioselectivity is lost due to the isolation of a mixture of both *cis* and *trans* regioisomers.[23]

The use of nitrone as a 1,3-dipole for cycloaddition processes dominates nitrone chemistry. Nitrone cycloaddition has been utilized to develop a number of natural products, versatile synthetic intermediates and biologically interesting compounds.[29,30] Aside from a vast range of five membered heterocycles created using nitrone cycloaddition, there are fewer reports on the synthesis of polymeric compounds utilizing nitrones *via* this approach.[31–33] Furthermore, only a few studies report the synthesis of bis-nitrones and their usage as a dipole substrate to synthesize macro sized molecules. The use of nitrones in polymer synthesis dates back to 1971, when Manecke *et al.*[34] for the first time reported the synthesis of α-(*p*-maleinimidophenyl)-*N*-(phenylnitrone) that was subjected to dipolar cycloaddition with the maleinimido group in the same molecule and this upon repeated addition led to the formation of macromolecules. Later, Heaney *et al.* in 2001 (ref. 35) and Vretik *et al.* in 2003,[36] reported the synthesis of bisisoxazolidines from bisnitrones and bis-maleimides. However, an insight into the surveyed literature showed that the usage of glyoxal bis-nitrones in the construction of macromolecules has not been described so far. Only a single paper by Chakraborty *et al.*[37] in 2014 reported the preliminary results for the synthesis of bisisoxazolidines from glyoxal derived nitrones. Although the authors reported the synthesis in water, the reaction time is too long *i.e.* 3–5 hours, whereas with the current protocol, bis pyrrolo isoxazoles were obtained within 10–15 minutes of addition of glyoxal solution to an aqueous solution of *in situ* generated phenylhydroxyl amines. The crude bis pyrrolo isoxazole product is insoluble, and precipitated out of the aqueous medium in 10–15 min. Moreover, the authors reported the synthesis of glyoxal-based bis-nitrones in organic solvents, whereas in the present study the same has been obtained by the condensation of glyoxal with *in situ* generated phenylhydroxyl amines. In the present case, a thermodynamically more stable regioisomer *i.e.* the *trans* cycloadduct has been formed.

Thus, with the aim of and in continuation to our interest to develop hetero-structures incorporating isoxazolidine rings,[23,27,38] the current study reports the synthesis of some novel symmetrical bis-pyrrolo isoxazoles *via* thermal 1,3-dipolar cycloaddition of glyoxal bis-nitrones with N-substituted maleimides. The glyoxal-based bis nitrones were synthesized by condensation of glyoxal with *N*-phenyl hydroxylamines in an aqueous medium only. And the cycloadditions too were performed in aqueous media. The formation of all the products is supported by spectral studies such as FTIR, NMR, elemental analysis, and mass spectrometry.

2. Experimental

2.1. General

The melting points reported here are uncorrected. All the chemicals used in the present study were of analytical grade and used without any further purification. FTIR spectra were recorded on a Bruker Alpha-T FTIR spectrophotometer. NMR analysis of the synthesized compounds was performed using a Bruker Avance-II 500 MHz FTNMR spectrometer, with tetramethylsilane as the internal standard. The mass spectral analysis was performed using an LCMS model LTQ-XL, from Thermo Scientific. Elemental analysis of the compounds was performed on an Elementar Vario MICRO cube CHN analyzer. Monitoring of the reaction was performed using TLC plates coated with silica gel (G254 grade). As the bis nitrones and bis isoxazolidine compounds synthesized are symmetrical, NMR spectral data for half of the structures are reported. To get the exact number of protons and carbon atoms, one needs to multiply by a factor of 2 in each case.

2.2. General procedure for the synthesis of nitrones (azomethine *N*-oxides)

For the synthesis of azomethine *N*-oxide, the partial reduction of nitrobenzene has been carried out at 60–70 °C under aqueous conditions. For this, 4 mL (42 mmol) of nitrobenzene was added to a beaker containing 100 mL water, followed by addition of 2.5 g of NH_4Cl (45 mmol). Thereafter, a pinch of Zn dust (out of the total 6 g, 84 mmol) was added to it and the contents were stirred mechanically. Zn dust (6 g) was added in portions to avoid an increase in temperature above 70 °C. The reduction is completed when no more nitrobenzene seems to be floating on the water surface. The filtrate is separated from solid ZnO and it was cooled to room temperature. A stoichiometric amount of glyoxal solution (3 mL, 40%) was added to the filtrate and stirred. Nitrone of glyoxal precipitated out as a yellow solid in just 15–20 min. The solid was then filtered, dried and recrystallized from chloroform. The formation of nitrone products was confirmed by their spectral and elemental analyses.

2.2.1 The spectral data for all the synthesized nitrones

2.2.1.1 Bis(N-phenyliminium)ethane-N,N′-dioxide. Yellow solid, mp 165–66 °C; FTIR (ν cm^{-1}): 1706, 1783 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.27–7.41 (m, 5H); 7.88 (s, 1H, –CH=N); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 123.8, 129.1, 134.7, 143.8; MS: *m*/*z*: 240 $[M]^+$; anal. calcd for $C_{14}H_{12}N_2O_2$: C, 70.00; H, 5.00; N, 11.67, found: C, 69.79; H, 4.91; N, 11.56.

2.2.1.2 Bis(N-tolyliminium)ethane-N,N′-dioxide. Light-yellow solid, mp 140–42 °C; FTIR (ν cm^{-1}): 1706, 1783 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 2.23 (s, 3H); 7.27 (m, 2H, Ar–H); 7.64 (m, 2H, Ar–H); 7.86 (s, 1H, –CH=N); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 17.6, 123.7, 128.4, 143.6, 144.4; MS: *m*/*z*: 268 $[M]^+$; anal. calcd for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97; N, 10.44, found: C, 71.15; H, 5.99; N, 10.32.

2.2.1.3 Bis(N-4-chlorophenyliminium)ethane-N,N′-dioxide. Light-yellow solid, mp 207–08 °C; FTIR (ν cm^{-1}): 1706, 1783 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.33 (m, 2H, Ar–H); 7.82 (m, 2H, Ar–H); 7.89 (s, 1H, –CH=N); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 123.7, 129.8, 145.9, 146.3; MS: *m*/*z*: 309 $[M]^+$; anal. calcd for $C_{14}H_{10}Cl_2N_2O_2$: C, 54.37; H, 3.24; N, 9.06, found: C, 54.04; H, 3.18; N, 9.26.

2.3. General procedure for synthesis of *N*-arylmaleimide

50 mmol each of maleic anhydride and amine were dissolved separately in 50 mL toluene and then mixed at room

temperature to obtain the corresponding maleamic acid. In the next step, the obtained maleamic acid was filtered, dried and converted to maleimide in the presence of 10 mmol of anhydrous sodium acetate in acetic anhydride (20 mL). The contents were refluxed on a boiling water bath for 1.5 hour and then poured onto ice-cold water taken in a beaker. The white precipitates of maleimide were filtered and dried.

2.4. General procedure for the cycloaddition reaction

To the aqueous solution of bis-nitrone of glyoxal (~5 mmol) (**1**), 10 mmol of *N*-arylmaleimide (**2**) were added and the contents of the flask were refluxed at 70 °C after being equipped with a reflux water condenser. Just after refluxing for 10–15 min, a white solid separated out of the mixture. The white precipitates of the cycloadduct were filtered and further purified through recrystallization from an ethanol–water (1 : 1) mixture.

2.5. The spectral data for the various cycloadducts

As the bis pyrroloisoxazole compounds synthesized are symmetrical, NMR spectral data for half of the structures are reported. To get the exact number of protons and carbon atoms, one needs to multiply by a factor of 2 in each case.

2.5.1 Compound (3a). White solid (0.67 g, 84%), mp 285–286 °C; FTIR (ν cm^{-1}): 1709, 1780 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 3.87 (d, 1H); 4.59 (s, 1H); 5.21 (d, 1H); 6.97–7.24 (m, 10H); ^{13}C NMR (125 MHz, d_6-DMSO), δ: 51.5, 69.0, 72.8, 112.9, 121.9, 126.9, 128.1, 128.5, 134.3, 149.0, 173.6, 174.4; MS: *m*/*z*: 586 $[M]^+$; anal. calcd for $C_{34}H_{26}N_4O_6$: C, 69.62; H, 4.47; N, 9.55, found: C, 70.19; H, 4.59; N, 9.51.

2.5.2 Compound (3b). White solid (0.76 g, 88%), mp 280–281 °C; FTIR (ν cm^{-1}): 1713, 1784 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 2.12 (s, 3H); 3.83 (d, 1H); 4.66 (s, 1H); 5.14 (d, 1H); 6.93–7.31 (m, 9H); ^{13}C NMR (125 MHz, d_6-DMSO), δ: 17.4, 54.8, 65.2, 72.3, 123.3, 124.9, 125.7, 126.1, 129.5, 133.4, 136.0, 172.8, 173.9; MS: *m*/*z*: 614 $[M]^+$; anal. calcd for $C_{36}H_{30}N_4O_6$: C, 70.35; H, 4.92; N, 9.12, found: C, 71.09; H, 4.90; N, 9.14.

2.5.3 Compound (3c). White solid (0.90 g, 84%), mp 291–292 °C; FTIR (ν cm^{-1}): 1706, 1784 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 3.9 (d, 1H); 4.1 (s, 1H); 4.79 (d, 1H); 7.08–7.38 (m, 9H); ^{13}C NMR (125 MHz, d_6-DMSO), δ: 51.6, 67.5, 77.8, 113.6, 126.0, 128.7, 128.9, 129.0, 131.4, 138.1, 146.9, 173.2, 174.4; MS: *m*/*z*: 655 $[M]^+$; anal. calcd for $C_{36}H_{30}N_4O_6Cl_2$: C, 63.07; H, 4.41; N, 8.17, found: C, 62.89; H, 4.33; N, 8.15.

2.5.4 Compound (3d). White solid (0.77 g, 87%), mp 272–273 °C; FTIR (ν cm^{-1}): 1714, 1781 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 3.83 (d, 1H, J = 7.76 Hz); 4.66 (s, 1H); 5.14 (d, 1H, J = 7.72 Hz); 6.84–7.23 (m, 9H); ^{13}C NMR (125 MHz, d_6-DMSO), δ: 19.1, 56.5, 65.3, 72.9, 123.3, 124.9, 125.7, 126.2, 129.4, 133.5, 134.7, 172.9, 174.0; MS: *m*/*z*: 614 $[M]^+$; anal. calcd for $C_{36}H_{30}N_4O_6$: C, 70.35; H, 4.92; N, 9.12, found: C, 70.71; H, 4.93; N, 9.04.

2.5.5 Compound (3e). White solid (0.89 g, 90%), mp 267–268 °C; FTIR (ν cm^{-1}): 1714, 1782 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 2.12 (s, 3H); 3.86 (d, 1H); 4.51 (s, 1H); 5.03 (d, 1H); 6.90–7.28 (m, 8H); ^{13}C NMR (125 MHz, d_6-DMSO), δ: 17.8, 19.5, 56.7, 65.8, 73.0, 123.3, 124.5, 125.1, 129.9, 133.5, 134.9, 173.4, 174.1; MS: *m*/*z*: 642 $[M]^+$; anal. calcd for $C_{38}H_{34}N_4O_6$: C, 71.01; H, 5.33; N, 8.72, found: C, 70.86; H, 5.29; N, 8.75.

2.5.6 Compound (3f). White solid (1.03 g, 82%), mp 274–275 °C; FTIR (ν cm^{-1}): 1709, 1783 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 3.81 (d, 1H, J = 7.28 Hz); 4.52 (s, 1H); 5.22 (d, 1H, J = 7.36 Hz); 6.93–7.28 (m, 8H); ^{13}C NMR (125 MHz, d_6-DMSO), δ: 17.6, 54.9, 63.7, 71.5, 124.3, 125.6, 126.2, 127.4, 128.9, 133.5, 134.9, 171.7, 173.9; MS: *m*/*z*: 683 $[M]^+$; anal. calcd for $C_{36}H_{28}N_4O_6Cl_2$: C, 63.26; H, 4.13; N, 8.20, found: C, 63.51; H, 4.11; N, 8.17.

2.5.7 Compound (3g). White solid (0.73 g, 88%), mp 264–265 °C; FTIR (ν cm^{-1}): 1714, 1784 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 3.83 (d, 1H); 4.22 (s, 2H); 4.66 (s, 1H); 5.14 (d, 1H); 6.90–7.28 (m, 10H); ^{13}C NMR (125 MHz, d_6-DMSO), δ: 14.2, 23.2, 46.1, 60.4, 113.7, 126.6, 127.7, 128.9, 129.1, 171.6; MS: *m*/*z*: 614 $[M]^+$; anal. calcd for $C_{36}H_{30}N_4O_6$: C, 70.35; H, 4.92; N, 9.12, found: C, 70.55; H, 4.92; N, 9.07.

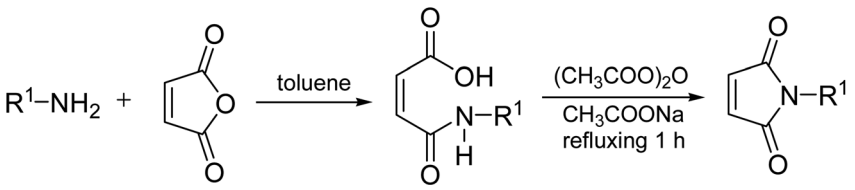
2.5.8 Compound (3h). White solid (0.89 g, 90%), mp 269–270 °C; FTIR (ν cm^{-1}): 1715, 1784 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 2.99 (s, 3H); 3.84 (d, 1H); 4.10 (s, 2H); 4.61 (s, 1H); 5.18 (d, 1H); 7.00–7.37 (m, 9H); ^{13}C NMR (125 MHz, d_6-DMSO), δ: 20.9, 26.9, 48.3, 56.2, 114.0, 127.3, 127.5, 128.3, 128.6, 129.0, 131.8, 148.1, 173.2, 174.9; MS: *m*/*z*: 642 $[M]^+$; anal. calcd for $C_{38}H_{34}N_4O_6$: C, 71.01; H, 5.33; N, 8.72, found: C, 70.83; H, 5.35; N, 8.74.

2.5.9 Compound (3i). White solid (1.05 g, 86%), mp 295–296 °C; FTIR (ν cm^{-1}): 1710, 1781 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 3.86 (d, 1H); 4.22 (s, 2H); 4.66 (s, 1H); 5.14 (d, 1H); 6.84–7.32 (m, 9H); ^{13}C NMR (125 MHz, d_6-DMSO), δ: 27.4, 31.9, 54.9, 63.6, 124.4, 125.1, 126.3, 127.0, 128.7, 129.0, 133.5, 171.9, 174.1; MS: *m*/*z*: 683 $[M]^+$; anal. calcd for $C_{36}H_{28}N_4O_6Cl_2$: C, 63.26; H, 4.13; N, 8.20, found: C, 63.46; H, 4.09; N, 8.16.

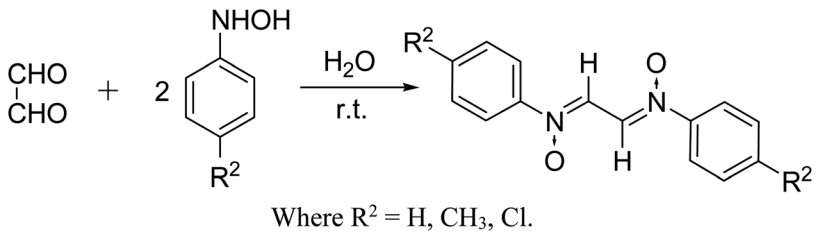
2.5.10 Compound (3j). White solid (0.72 g, 88%), mp 290–291 °C; FTIR (ν cm^{-1}): 1706, 1781 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.04–1.76 (m, 7H), 1.7 (m, 2H), 2.7 (m, 2H), 3.83 (d, 1H); 4.28 (s, 1H); 4.81 (d, 1H); 6.95–7.67 (m, 5H); ^{13}C NMR (125 MHz, d_6-DMSO), δ: 18.4, 19.8, 20.5, 51.6, 52.0, 55.9, 67.5, 68.2, 77.8, 78.4, 118.7, 129.0, 129.3, 129.4, 147.4, 171.9, 173.8; MS: *m*/*z*: 598 $[M]^+$; anal. calcd for $C_{34}H_{38}N_4O_6$: C, 68.21; H, 6.40; N, 9.36, found: C, 68.37; H, 6.44; N, 9.38.

2.5.11 Compound (3k). White solid (0.81 g, 84%), mp 291–292 °C; FTIR (ν cm^{-1}): 1714, 1784 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.04–1.38 (m, 5H), 1.50–1.68 (m, 2H), 1.73 (m, 2H); 2.52 (s, 2H), 2.89 (s, 3H); 3.83 (d, 1H); 4.66 (s, 1H); 5.21 (d, 1H); 6.93–7.21 (m, 4H); ^{13}C NMR (125 MHz, d_6-DMSO), δ: 17.9, 24.8, 26.1, 28.5, 28.8, 52.3, 53.4, 65.0, 123.5, 125.2, 126.4, 132.6, 172.7, 173.8; MS: *m*/*z*: 626 $[M]^+$; anal. calcd for $C_{36}H_{42}N_4O_6$: C, 68.99; H, 6.75; N, 8.94, found: C, 69.17; H, 6.71; N, 9.00.

2.5.12 Compound (3l). White solid (0.91 g, 80%), mp 297–298 °C; FTIR (ν cm^{-1}): 1714, 1785 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.04–1.22 (m, 5H), 1.37–1.58 (m, 2H), 1.73–1.80 (m, 2H); 2.66 (m, 2H); 3.83 (d, 1H); 4.59 (s, 1H); 5.14 (d, 1H); 7.06–7.52 (m, 4H); ^{13}C NMR (125 MHz, d_6-DMSO), δ: 26.1, 30.6, 34.9, 48.4, 60.0, 65.4, 109.2, 129.0, 129.5, 131.3, 141.2, 178.4; MS: *m*/*z*: 667 $[M]^+$; anal. calcd for $C_{34}H_{36}N_4O_6Cl_2$: C, 61.17; H, 5.44; N, 8.39, found: C, 60.99; H, 5.39; N, 8.43.



Scheme 1 Synthesis of N-substituted maleimide.



Scheme 2 Synthesis of bis azomethine *N*-oxides.

3. Results and discussion

3.1. Synthesis

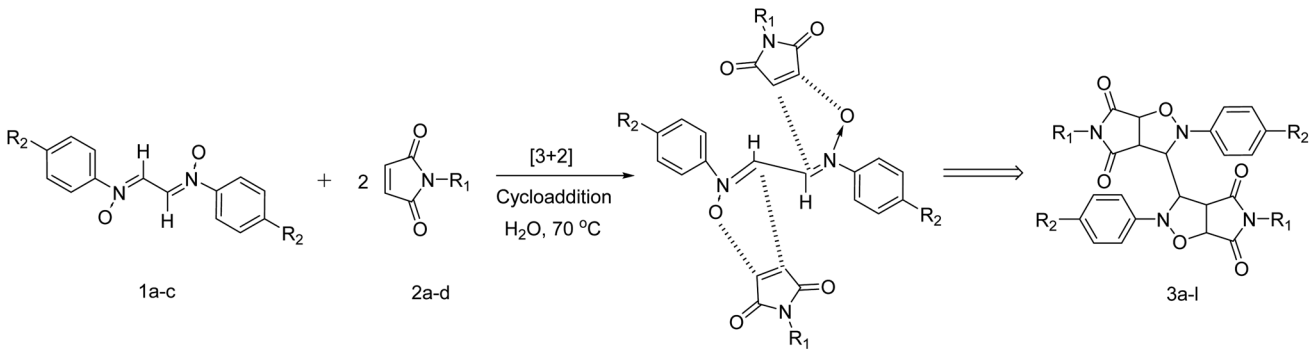
Initially, the dipolarophile maleimides to be used in this cycloaddition were synthesized using a process similar to that described in the literature.[39] The condensation reaction between amines and maleic anhydride, followed by dehydration using sodium acetate and anhydrous acetic anhydride afforded cyclised maleimides (Scheme 1). The formation of the maleimide products has been confirmed on the basis of their melting points (compared with that of authentic samples) and by comparing their spectral data.[39]

Another reactant *i.e.* bis-nitrones, to be used in the 1,3-dipolar cycloadditions, were synthesized by condensing glyoxal solution with the mono substituted phenyl hydroxylamines in a 1 : 2 ratio in an aqueous medium (Scheme 2). Phenyl hydroxylamines were prepared by the partial reduction of substituted nitrobenzene with zinc dust and ammonium chloride in an aqueous medium as described in the literature.[40] The subsequent condensation reaction of the above synthesized *N*-phenyl hydroxylamines with glyoxal solution in an aqueous medium afforded bis-nitrones (Table 1) as ascertained by their FTIR and ^{1}H-NMR analyses. All the bis-nitrones obtained were yellow in colour and were crystallized out of ethanol prior to their use in cycloadditions.

After synthesizing the reactants, their dipolar cycloaddition was performed in aqueous media at 70 °C. For this, a 2 equiv. of

Table 1 Characterisation data of bis azomethine *N*-oxides

Entry	R^2	% Yield	MP	Time (in min)	*m*/*z* (M^+)
1	H	92	165–66	15	240
2	CH_3	96	140–42	15	268
3	Cl	89	207–08	20	309



Scheme 3 Synthesis of symmetrical bis isoxazolidines.

Table 2 Synthesis of bis pyrroloisoxazole cycloadducts

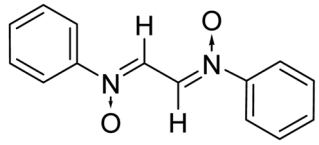
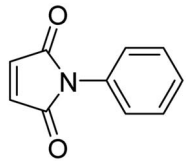
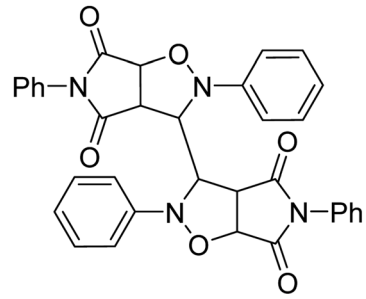
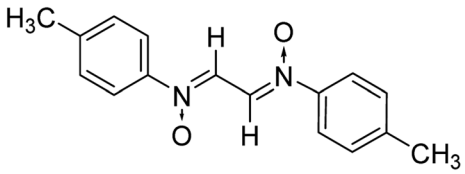
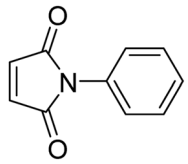
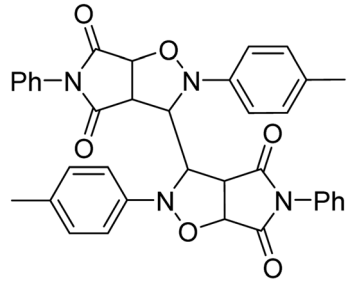
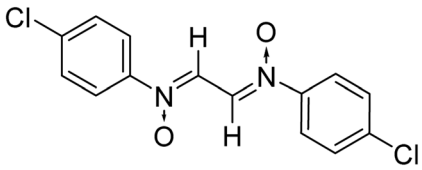
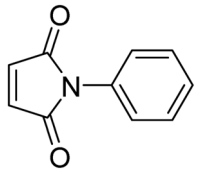
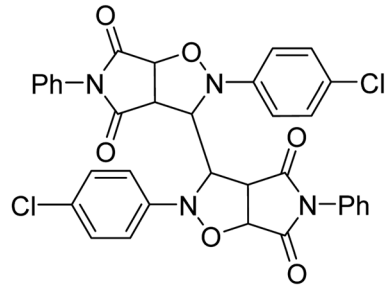
Entry	Nitrone	Maleimide	Product	Time (min)	% Yield	MP
1			 (3a)	10	84	285–286
2			 (3b)	10	88	280–281
3			 (3c)	12	84	291–292

Table 2 (*Contd.*)

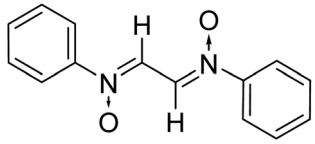
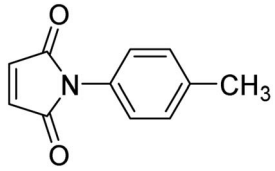
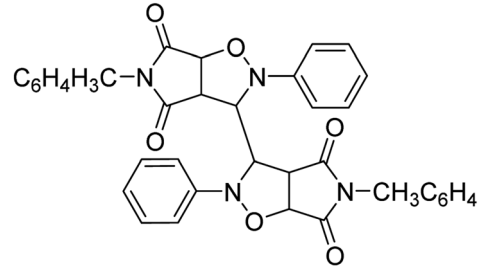
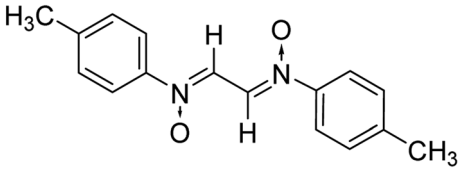
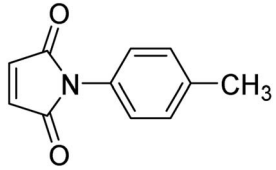
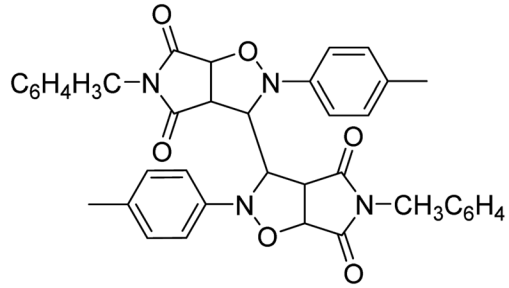
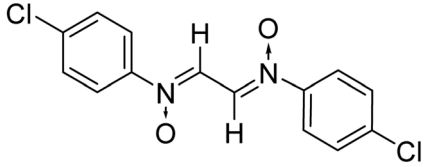
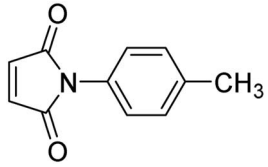
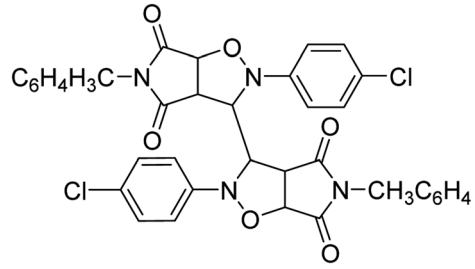
Entry	Nitrone	Maleimide	Product	Time (min)	% Yield	MP
4			 **(3d)**	10	87	272–273
5			 **(3e)**	10	90	267–268
6			 **(3f)**	14	82	274–275

Table 2 (*Contd.*)

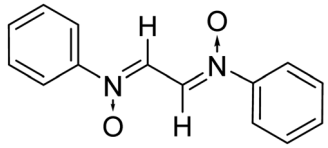
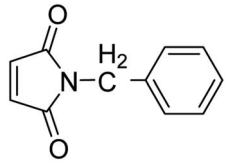
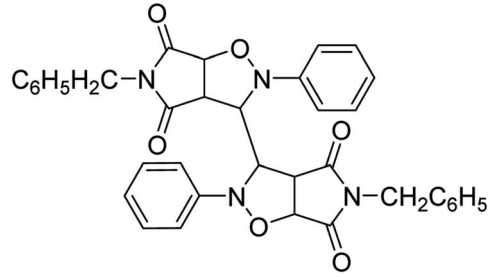
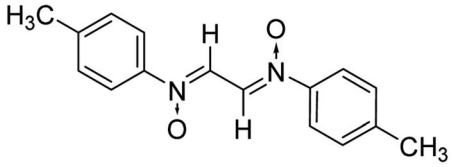
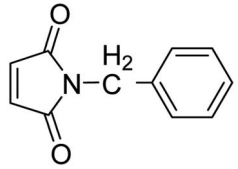
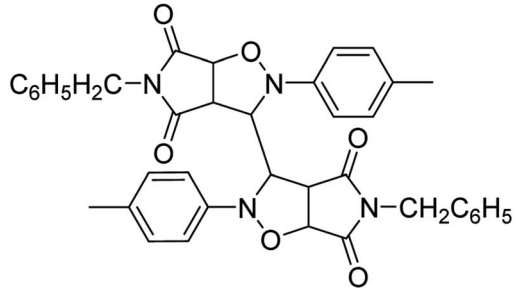
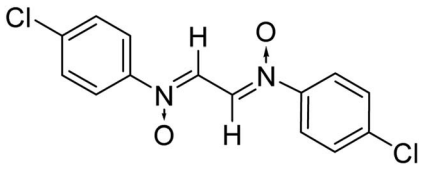
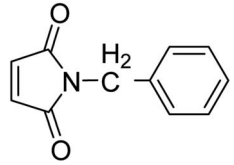
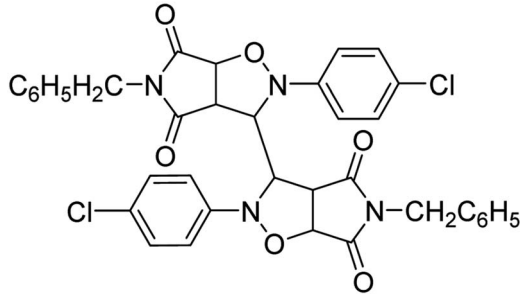
Entry	Nitrone	Maleimide	Product	Time (min)	% Yield	MP
7			 **(3g)**	10	88	264–265
8			 **(3h)**	10	90	269–270
9			 **(3i)**	12	86	295–296

Table 2 (*Contd.*)

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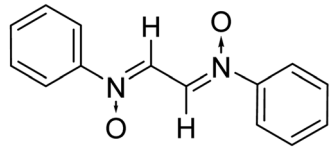
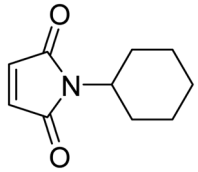
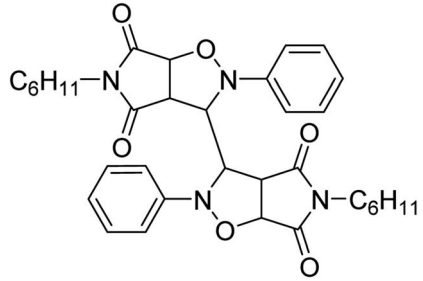
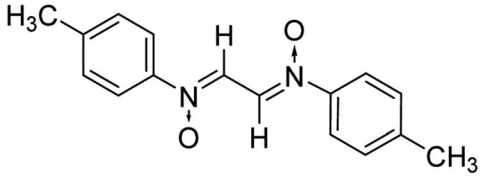
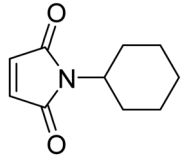
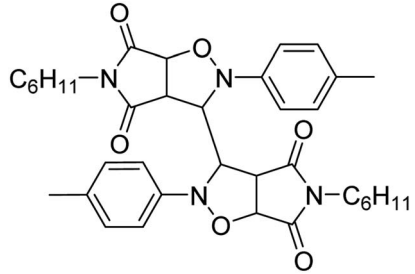
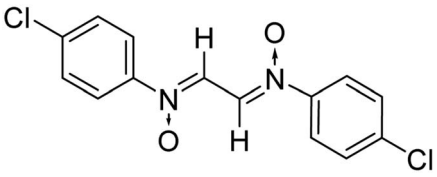
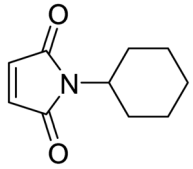
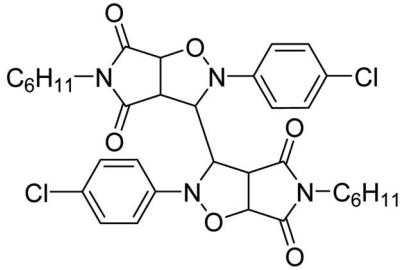
10			 **(3j)**	12	88	290–291
11			 **(3k)**	12	84	291–292
12			 **(3l)**	15	80	297–298

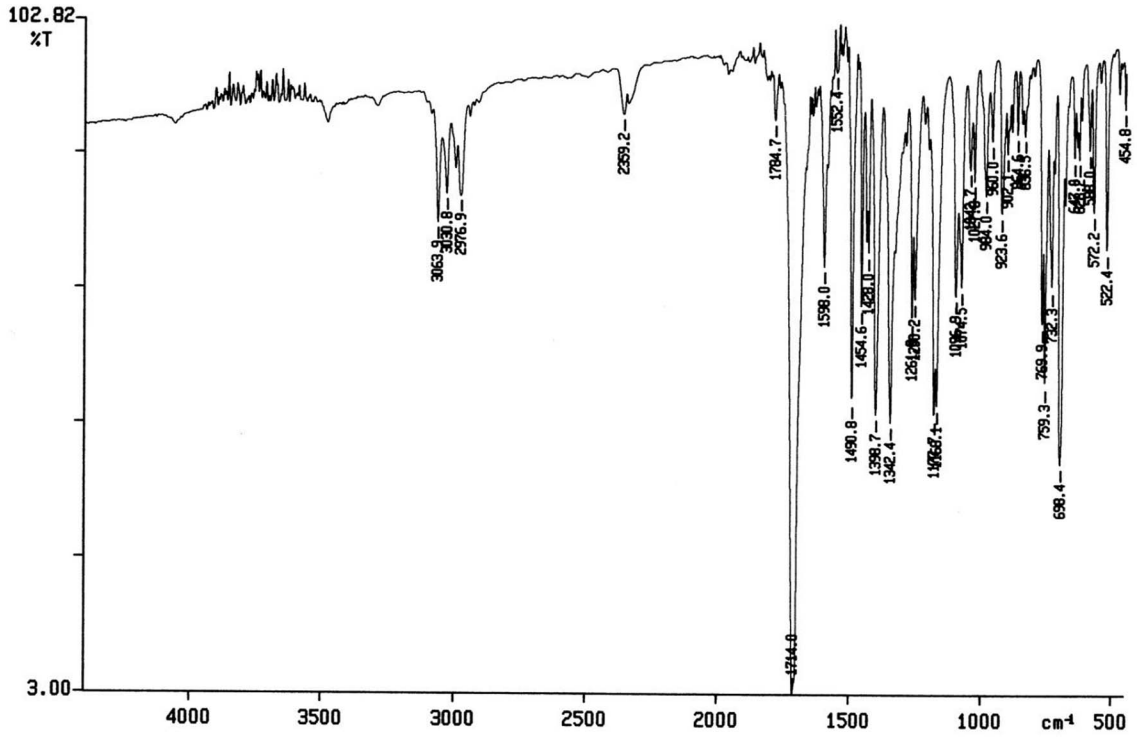


Fig. 1 FTIR spectrum of the synthesized compound **3g**.

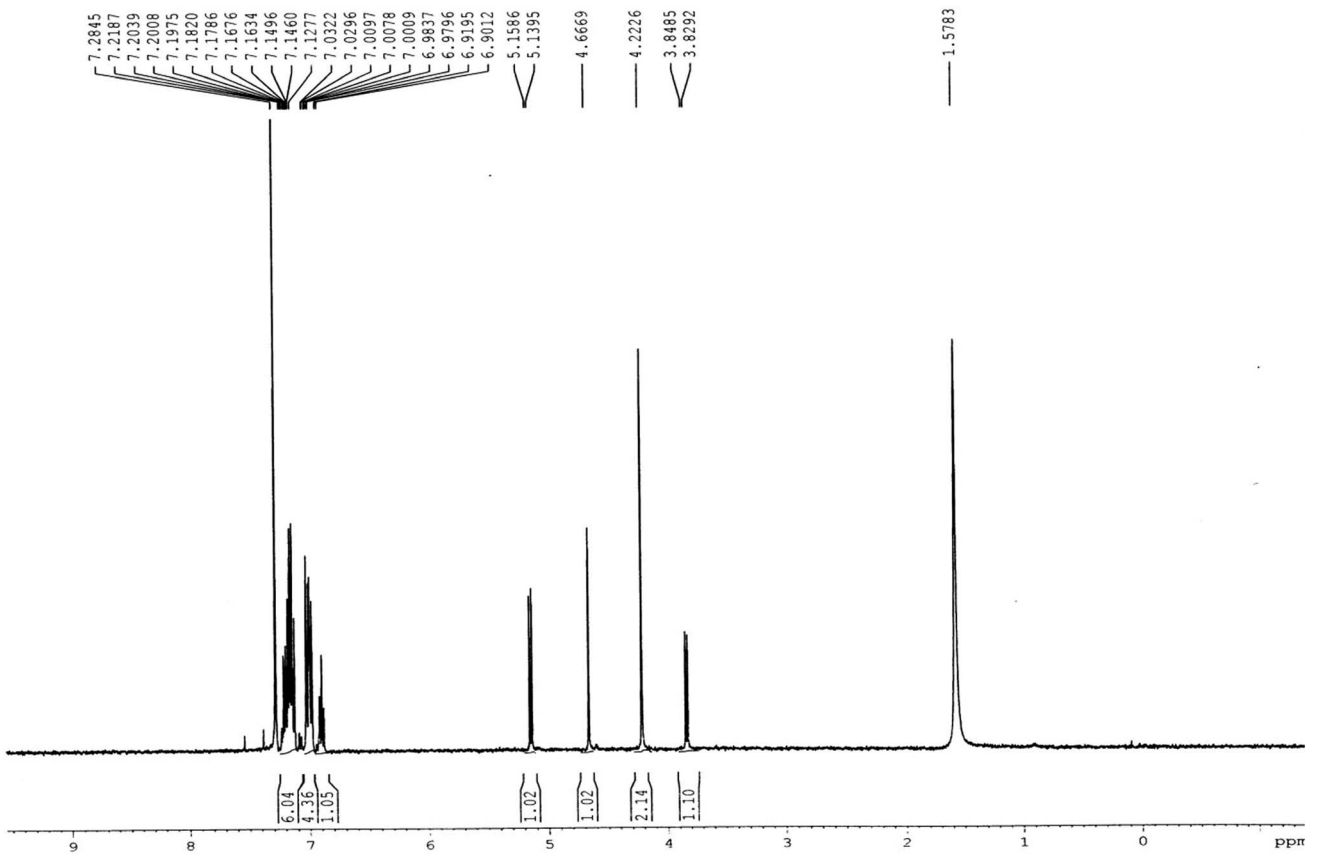


Fig. 2 ^{1}H NMR spectrum of the synthesized compound **3g**.

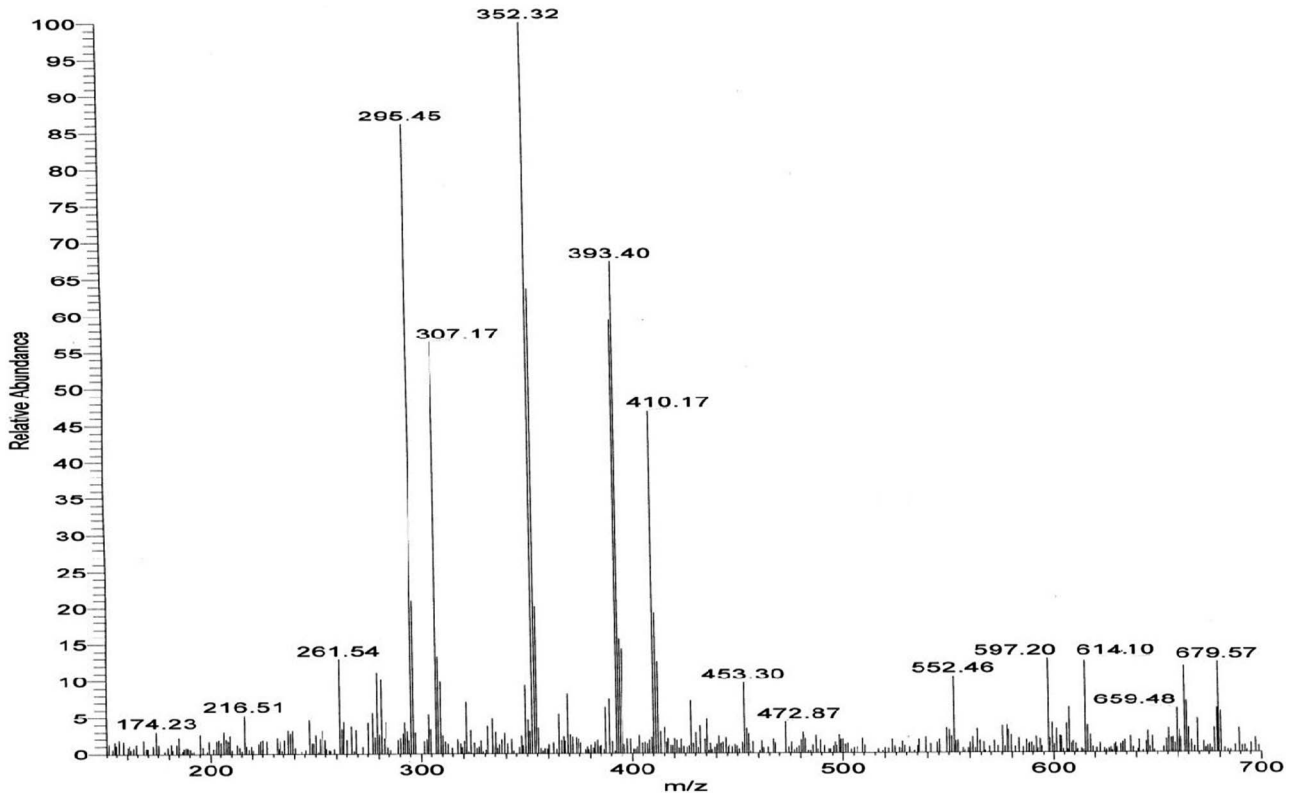


Fig. 3 Mass spectrum of the synthesized compound **3g**.

N-aryl maleimide were added to an aqueous solution of bis-nitrones of glyoxal and heated to 70 °C (Scheme 3). Upon refluxing for just 15–20 min, a solid appeared in the flask. The white solid thus obtained was filtered, purified and dried *in vacuo* and subjected to spectral analysis.

The products have been characterized as bis *trans*-2,5-diaryl-pyrroloisoxazole-4,6-diones (Table 2) through their melting point, and FTIR, NMR, mass spectral and elemental analyses. The position of the C_3–H proton in relation to the C_{3a}–H and C_{6a}–H protons in the ^{1}H-NMR spectrum was used to ascribe the *trans* configuration to these products. Furthermore, the C_3–H and $C_{3'}$–H protons were also found to be *trans* to each other, which may be due to steric reasons. However, no product with a *cis* configuration was isolated.

3.2. Spectral studies

The spectral data of one of the synthesized compounds, pyrrolo isoxazole **3g** are described here. In the infrared absorption spectrum of compound **3g** (Fig. 1), an absorption band in the region of 3063–2977 cm^{-1} has been linked to the C–H stretching vibration. Two absorption bands at 1784 and 1714 cm^{-1} correspond to the two carbonyls of the succinimide moiety. The absorption bands due to the C=C bond of the aromatic ring and C–N bond appeared at 1598 cm^{-1} and 1398 cm^{-1}, respectively. The C–O bond stretching appeared in the form of medium intensity bands at 1261 and 1181 cm^{-1}.

In the proton NMR spectrum of compound **3g** (Fig. 2), a doublet at δ 3.83 Hz was ascribed to the C_{3a}–H proton. The C_3–H proton appeared in the form of a singlet at δ 4.66 as it does not couple with the C_3–H of the other half of the molecule due to dihedral angle between the two. Another doublet at δ 5.14 (J = 7.64 Hz) has been assigned to the C_{6a}–H proton. The benzylic protons appeared in the form of a singlet at δ 4.22, while the multiplet of aromatic protons appeared between δ 6.9 to δ 7.3, in the NMR spectrum.

The mass spectra of the compound **3g** (Fig. 3) show a molecular ion peak at m/z 614, thereby confirming that the bis 1,3-dipolar cycloaddition has taken place. And since the

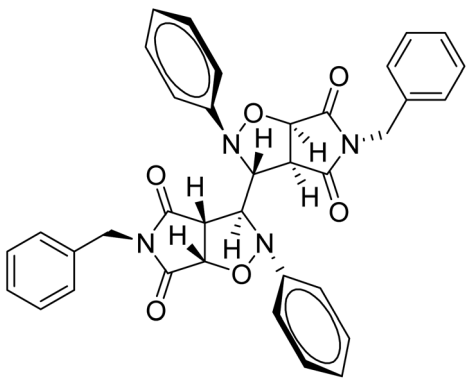


Fig. 4 Dreiding model of compound **3g** (*trans*).

molecule is symmetrical around one of the aliphatic carbons, a peak corresponding to half of the molecular mass *i.e.* at *m*/*z* 307, was also observed (Fig. 3).

Mechanistically, the formation of only a *trans* diastereoisomer (Fig. 4) can be explained on the basis of the *endo*-transition mode, in which the succinimide moiety and *N*-phenyl ring of the nitrone lie on the same side, and thus stabilizes the transition state due to maximum π–π overlap. These 1,3-dipolar cycloadditions provide *trans* diastereoisomer exclusively as the single product as steric interactions seem to be maximum in the transition state leading to the *cis* isomer. Moreover, the large sized bicyclic pyrrolo isoxazole moiety could not be on the same side due to steric hindrance as they are located on adjacent carbon atoms of the glyoxal precursor, which ruled out the formation of a *cis* isomer.

4. Conclusion

To sum up, the synthesis of bis-pyrrolo isoxazole cycloadducts reported here is facile, efficient, regioselective and eco-friendly. An attractive feature of this protocol is that it generates only the *trans* stereoisomer without the involvement of any chiral catalyst or specialised reaction conditions. The formation of only one *trans*-diastereoisomer was confirmed through IR and NMR spectroscopy. Moreover, the cycloadducts were formed in a very short interval of 15–20 minutes and that too under aqueous conditions. Further work to synthesize bis-pyrrolo isoxazoles replacing glyoxal nitrones with other bis dipole substrates is in progress.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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