Pergamon

Tetrahedron 57 (2001) 7951–7964

TETRAHEDRON

X=Y–ZH Systems as potential 1,3-dipoles. Part 53: Sequential nucleophilic ring opening-1,3-dipolar cycloaddition reactions of *Z*-oxime anions with aziridines and dipolarophiles☆

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Received 27 April 2001; revised 21 June 2001; accepted 19 July 2001

Abstract—Nucleophilic ring opening of aziridines involving attack of the nitrogen atom of *Z*-oxime anions generates nitrones which are then trapped in 1,3-dipolar cycloaddition reactions with *N*-methylmaleimide to afford 1:1 mixture of *endo*- and *exo*-cycloadducts. © 2001 Elsevier Science Ltd. All rights reserved.

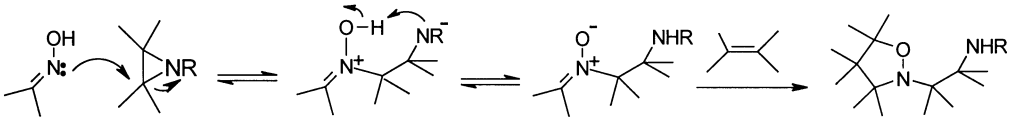
Ring opening of aziridines and aziridinium ions by various nucleophiles (e.g. alkoxides, nitrogen, sulfur, etc.) has been extensively studied[2–6] and aziridinium ion intermediates have been characterised.[7] Various catalysts have been reported to promote aziridine ring-opening and to improve the regioselectivity[2,7–9] of the process. Methods for the synthesis of enantiopure aziridines and their stereoselective ring-opening have considerably increased their synthetic utility.[10–12] It has also been reported that the enantioselectivity of the ring-opening reactions can be controlled by chiral copper catalysts.[13] We have shown regiospecific nucleophilic ring-opening reactions of epoxide by *Z*-oximes generates nitrones in good yield. The nitrones when trapped by dipolarophiles gave isoxazolidine also in good yield.[14,15]

To date oximes have not been used as nucleophiles in the ring opening reactions of aziridines. We now report that nucleophilic ring opening of aziridines by *Z*-oxime anions occurs under mild conditions to generate nitrones in good to excellent yield. The nitrones can then be reacted with dipolarophiles to give isoxazolidines in good to excellent yield (Scheme 1).

Z-Benzaldoxime (**1**) reacts with sodium hydride and the aziridine (**2**) in THF (rt, 18 h) to afford nitrone (**3**) in 61% yield. The nitrone upon heating in xylene (120°C, 20 h) with phenyl vinyl sulphone gave cycloadduct (**4**) as a single *endo*-isomer in 64% yield.

The stereochemistry of (**4**) was assigned on the basis of n.O.e data and 2D-COSY studies. In contrast, nitrone (**3**) when heated in xylene (120°C, 20 h) with *N*-methylmaleimide (NMM) gave a 1:1 mixture of *exo*-(**6**)- and *endo*-(**7**)-cycloadducts in 79% yield. The stereochemistry of (**6**) and (**7**) was determined from n.O.e. data and 2D-COSY studies. The formation of a single cycloadduct from (**3**) and phenyl vinyl sulphone reflects the greater steric demand of phenylsulphonyl group which disfavours the transition state leading to (**8**) (Scheme 2).

The *E*-benzaldoxime did not give the ring-opening reaction. This is ascribed to the steric hindrance of the nitrogen lone pair, by the phenyl ring, in the ring-opening transition state (Scheme 3). *Z*,*E*-Isomerisation must be effectively prohibited under the ring-opening reactions i.e. ambient



Scheme 1.

☆ See Ref. 1 for Part 52.

Keywords: aziridine ring-opening; aziridinium ion; *Z*-oximes; nitrones; 1,3-dipolar cycloaddition.
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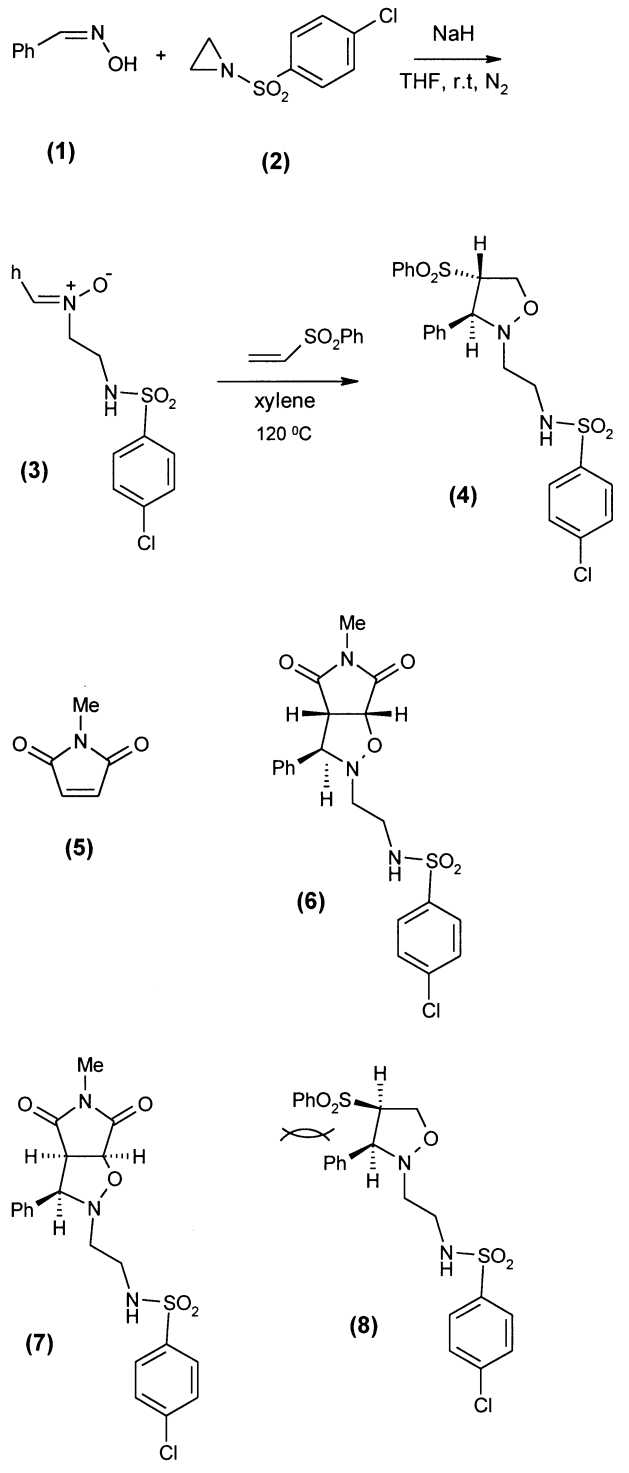
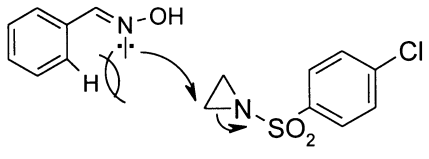
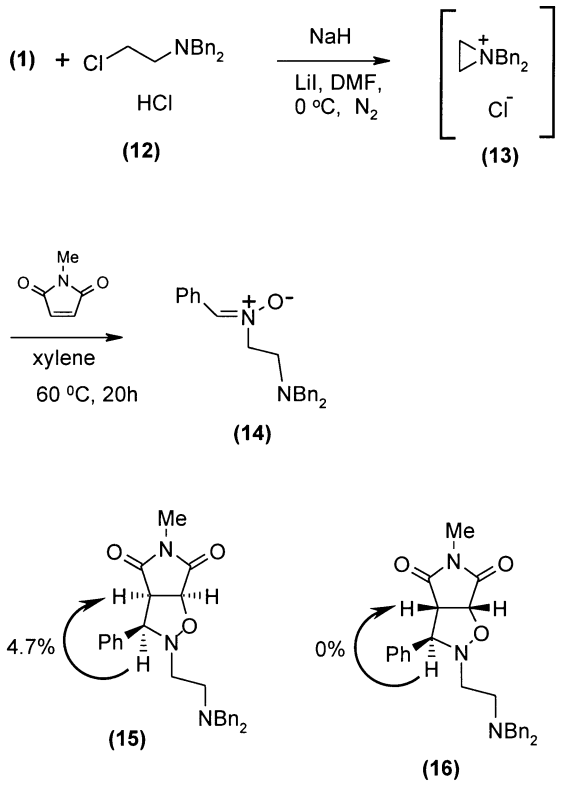
PII: S0040-4020(01)00767-0



Scheme 2.



Scheme 3.



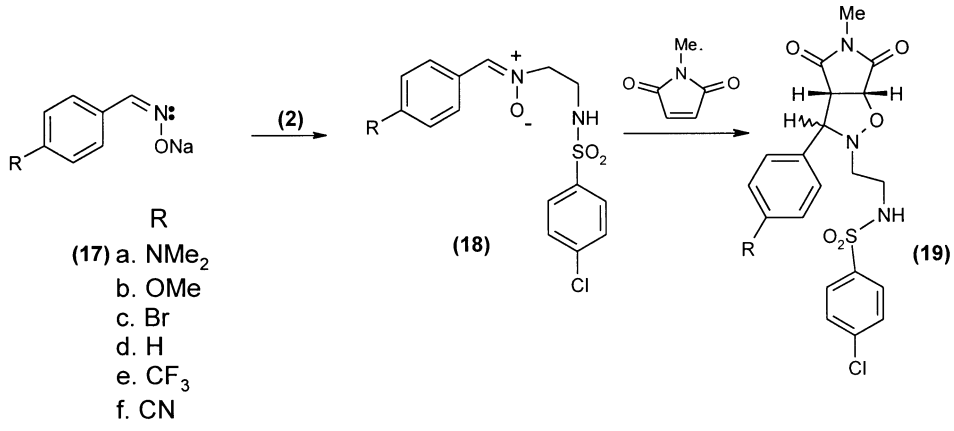
Scheme 4.

temperatures. This was also observed in the analogous epoxide-ring opening reactions.[14]

Nitrone formation also occurred when *Z*-benzaldoxime was reacted with 2-chloroethyl-*N*,*N*-dibenzylamine hydrochloride (**12**) in the presence of NaH and LiI at 0°C for 6 h. The nitrone (**14**) was heated in xylene with NMM at 60°C for 20 h to give a 1:2 mixture of *endo*-(**15**) and *exo*-(**16**) cycloadducts in 53% yield. The stereochemistry of the products was assigned on the basis of n.O.e. difference spectroscopy and 2D-COSY studies (Scheme 4).

A series of 4-substituted *Z*-aryl oxime sodium salts (**17**) were evaluated in the ring opening reaction (Scheme 5) and the results are collected in Table 1.

The isolated yield of nitrones increases from 45% with the most strongly electron-withdrawing group (Table 1, entry 6, R=CN) to 76% with 4-methoxy benzaldoxime (Table 1, entry 2). The substituent effect is not clear cut due to the reaction species being the oxime anion, the negative charge of which cannot be localised on the nitrogen atom but which clearly potentiates the nucleophilicity of the nitrogen-lone pair. The dimethylamino group is a strongly electron-donating moiety (Table 1, entry 1) and might be expected to give the highest yield of nitrone. The lower yield of nitrone (59%) in this case may be due to the nucleophilic lone pair on the amino nitrogen attacking the aziridine ring causing side reactions. The stereochemistry of the cycloadducts was determined from n.O.e. data and 2D-COSY studies and confirmed in the case of (**19**) by an X-ray crystal structure (Table 1, entry 2, R=OMe) (Fig. 1).



Scheme 5.

Table 1.

Entry	17(a–g) R	18(a–g) Nitrone (%)[a,b]	19(a–g) Isoxazolidine (%)[a,c]
1	NMe_2	59	81
2	Ome	76	91
3	Br	69	87
4	H	65	79
5	CF_3	58	92
6	CN	45	80
7	Cinnamaldoxime	75	57

[a] Isolated yield.
[b] Reactions carried out in THF, rt for 16 h.
[c] Reactions carried out in xylene at 140°C for 16 h. In each case a 1:1 mixture of *endo*- and *exo*-isomers was obtained.

Oxime (**20**) reacts with aziridine (**2**) in the presence of NaH (THF, rt, 18 h) to give nitrone (**21**) (75%). Heating nitrone (**21**) in xylene (120°C, 12 h) afforded a 1:1 mixture of *endo*-(**22**) and *exo*-(**23**) cycloadducts in 57% yield. Nitrone (**21**) when heated in xylene with phenyl vinyl sulphone (120°C, 18 h) resulted in 5:1:1 ratio of the *endo*-4-substituted isoxazolidine (**24**) and the *exo*-(**25**)- and *endo*-(**26**)-5-substituted isomers in 67% combined yield. The stereochemistry of (**22**)–(**26**) were determined from n.O.e. data and 2D-COSY studies (Scheme 6).

A series of *Z*-heteroaryl oxime anions (**27**) was utilised to effect aziridine ring opening (Scheme 7). The yield of nitrone (**28**) obtained from the standard reaction of the oxime anion with *N*-(-4-chlorophenylsulphonyl)aziridine increased from 56% in the case of furan, oxygen being the least electron-donating heteroatom, to 70% in the case of thiophene. However, the yield dropped to 53%, in the case of pyrrole, which is the most strongly electron-donating heterocycle (Table 2). This is may be due to deprotonation of the weakly acidic proton on the pyrrole nitrogen (p*K*a~16), by sodium hydride, generating a second ambident nucleophile. It was again noted that the yields of nitrones increased with the insertion of a double bond between the heteroaryl and oxime moieties (Table 2).

1,3-Dipolar cycloaddition of the nitrones, with NMM occurred smoothly to give the corresponding isoxazolidines (**29**) and (**30**) (Scheme 7) as mixtures of *endo*-and *exo*-isomers in good yields. Pyrrole nitrone (**28**, X=NH, *n*=1) did not undergo 1,3-dipolar cycloaddition with NMM even after prolonged reaction times. This is probably due to the formation of a stable 6,6-hydrogen bonded system (**31**) as can be seen in the crystal structure determined by X-ray diffraction studies (Fig. 2).

This new sequential process allows access to a range of novel isoxazolidines, in good yield, under mild conditions, from readily available starting materials.

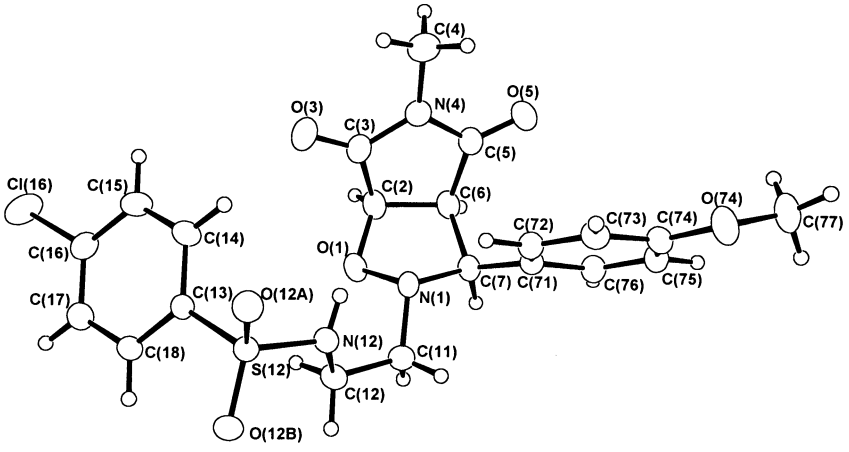
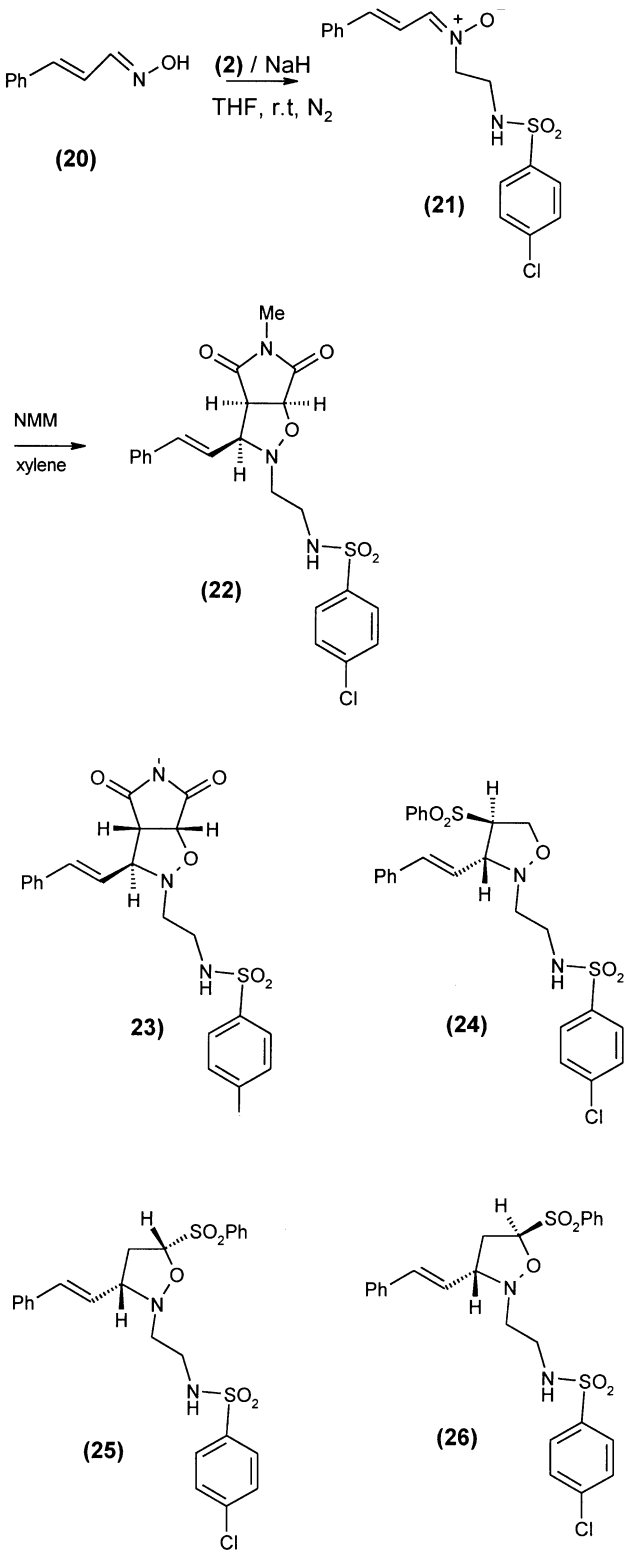


Figure 1. X-Ray crystal structure of (**19**).



Scheme 6.

1. Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H Nuclear magnetic resonance spectra were recorded at 300 MHz on a Bruker QE 300 instrument unless otherwise stated or at 400 MHz on a Bruker WP 400 instrument. Deuterochloroform was used as solvent unless stated otherwise, and chemical shifts (δ) are given in parts per million. ^{1}H Spectra are referenced to tetramethylsilane or residual protonated solvent. Assignments of ^{1}H signals were made with the aid of 2D-COSY spectra where necessary. Microanalyses were obtained using a Carlo Erba Elemental Analyser MOD 1106 instrument. Mass spectra were recorded on a VG-AutoSpec spectrometer using electron impact (EI) operating at 70 eV or by fast atom bombardment (FAB), as specified. IR spectra were performed on a Nicolet FT IR. A film of the analyte was depositied on a germanium crystal by evaporation of a dichloromethane solution. The following abbreviation are used: w=weak, m=medium, s=strong, br=broad. Flash column chromatography employed silica gel 60 (Merk 230–400 mesh) or Kieselgel 60 HF_{254}. Ether refers to diethyl ether and petroleum ether refers to the fraction with boiling point 40–60°C.

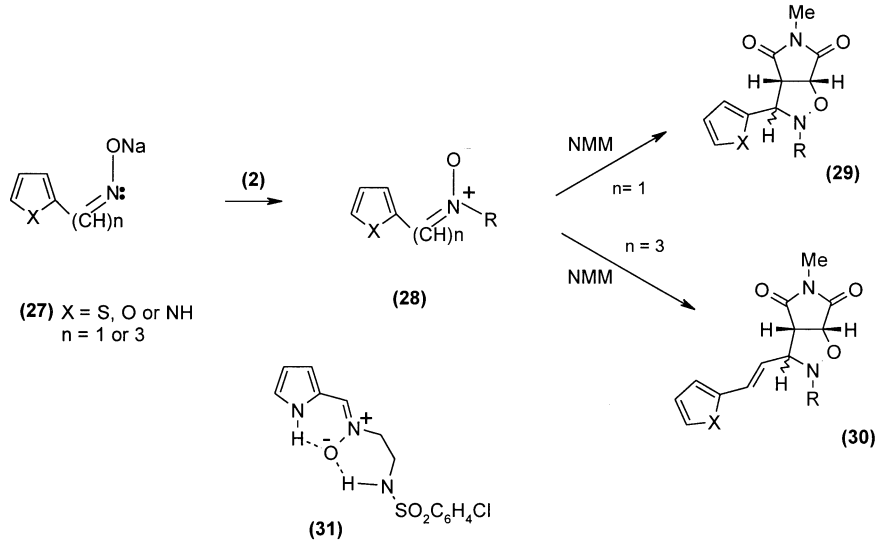
1.1. Synthesis of starting materials

The aryl oximes (**17**),[16a–f] (**27b**),[16g] and (**27d**)[16h] were prepared by standard procedures from aryl or heteroaryl aldehydes, hydroxylamine hydrochloride and sodium acetate, to give *E*-aldoximes. Conversion to the *Z*-isomers was effected by bubling dry hydrogen chloride gas through an etheral solution of the oxime, to precipitate the hydrochloride salt, followed by neutralisation of the salt by addition to a warm aqueous sodum bicarbonate solution.[16b] *Z*-Heteroaryl oximes (**27a**),[17a] (**27c**)[17b] and (**27e**)[17c] were synthesised by heating the appropriate heteroaryl-2-carboxaldehyde in pyridine, with hydroxylamine hydrochloride, under reflux for 1.5 h. The solvent was then removed under reduced pressure and the residue shaken vigorously with water to precipitate the *Z*-oxime. *N*-(4-Chlorophenylsulphonyl) aziridine and. *N*-(2-bromophenylsulphonyl)aziridine were prepared from the NH aziridine[18] and the appropriate arylsulphonyl chloride under basic conditions.[19]

1.2. General procedure for the preparation of nitrones

A solution of *Z*-oxime (2.5 mmol) and NaH (100 mg, 60% dispersion in mineral oil, 2.5 mmol) in dry THF (30 ml), were stirred for 20 min at room temperature under nitrogen. Then aziridine (0.65 g, 3 mmol) was added to the reaction mixture and the resulting solution stirred at room temperature for a further 14 h. THF was removed under reduced pressure, water (25 ml) added and the mixture extracted with DCM (5×20 ml). The combined organic layer was dried ($MgSO_4$), the solvent removed under reduced pressure, the residue washed with ether and the solid residue crystallised from ethyl acetate.

1.2.1. *C*-(4-Dimethylaminophenyl)-*N*-[2-(4′-chlorophenylsulphonamido)ethyl]nitrone (18a). Obtained as colourless needles from ethyl acetate (556 mg, 59%), mp 176–178°C. (Found: C, 53.4; H, 5.0; N, 11.25; S, 8.3. $C_{17}H_{20}ClN_3O_3S$ requires: C, 53.45; H, 5.3; N, 11.0; S, 8.4%); δ: 3.03 (s, 6H, Me_2N), 3.40 (m, 2H, CH_2NH), 3.95 (m, 2H, CH_2N^+), 6.65 (m, 3H, 2ArH+NH), 7.23 (s, 1H, CH=N^+), 740, 7.80 and 8.05 (3×d, J=8.1 Hz, 3×2ArH). ν_{max} (film): 3000 (br, CH, NH), 1604 (C=N), 1523, 1366, 1328, 1160, 1094, 821 and



Scheme 7.

Table 2.

Entry	X/*n*	**28**(**a**–**e**) (%)[a,b]	(**29a**–**e**):(**30a**–**e**)	(**29**)/(**30**) (%)[a,c]
1	NH/1	53	–	–
2	S/3	86	1:1	82
3	S/1	70	1:1	68
4	O/3	70	1:1	78
5	O/1	56	2:1	74

[a] Isolated yield.
[b] Reactions carried out in THF, at rt for 16 h.
[c] Reactions carried out in xylene at 140°C for 16 h.

725 cm^{-1}. *m*/*z*(%) 381 (M+, 7), 365 (7), 161 (100), 148 (40) and 134 (22).

1.2.2. *C*-(4-Methoxyphenyl)-*N*-[2-(4′-chlorophenylsulphonamido)ethyl]nitrone (18b). Obtained as colourless needles from ethyl acetate (710 mg, 76%), mp 187–189°C. (Found: C, 52.4; H, 4.7; N, 7.55; S, 8.6. $C_{16}H_{17}ClN_2O_4S$ requires: C, 52.1; H, 4.65; N, 7.6; S, 8.7%); δ: 3.45 (t, 2H, *J*=5.0 Hz, CH_2NH), 3.80 (s, 3H, OMe), 4.0 (t, 2H, *J*=5.0 Hz, CH_2N^+), 6.20 (br, 1H, NH), 6.90 (d, *J*=8.0 Hz, 2H, ArH), 7.25 (s, 1H, CH═N^+), 7.46, 7.80 and 8.14 (3×d, *J*=8.0 Hz, 3×2ArH). ν_{max} (film): 3000 (br, CH, NH), 1600 (C═N), 1507, 1331, 1251, 1149, 1094, 824 and 759 cm^{-1}. *m*/*z*(%) 368(M^+, 13), 193 (42), 175(24), 148 (100), 135 (51), 121 (66) and 111 (39).

1.2.3. *C*-(4-Bromophenyl)-*N*-[2-(4′-chlorophenylsulphonamido)ethyl]nitrone (18c). Obtained as colourless needles from ethyl acetate (720 mg, 69%), mp 203–204°C. (Found: C, 43.1; H, 3.35; N, 6.45; S, 7.6. $C_{15}H_{14}BrClN_2O_3S$ requires: C, 43.15; H, 3.4; N, 6.7; S, 7.7%); δ: 3.50 (m, 2H, CH_2NH) 4.05 (t, *J*=5.1 Hz, 2H, CH_2N^+), 5.87 (t, *J*=5.9 Hz, 1H, NH), 7.24 (s, 1H, CH═N^+) and 7.40–8.05 (4×d, *J*=8.0 Hz, 4×2ArH). ν_{max} (film): 3100 (br, CH, NH), 1586 (C═N),

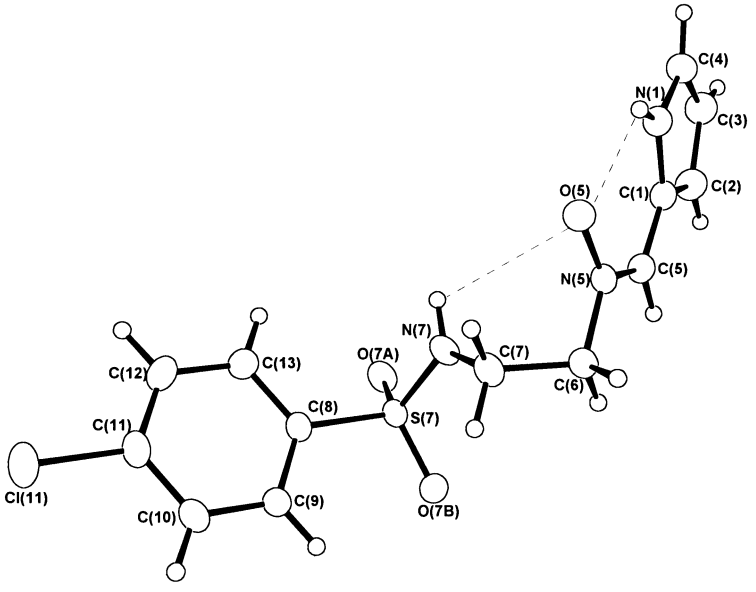


Figure 2. X-Ray crystal structure of (**31**).

1477, 1424, 1396, 1329, 1157, 1095, 825 and 755 cm^{-1}. *m/z*(%) 418 (M^+, 3), 241 (19), 198 (100), 175 (54) and 111(83).

1.2.4. *C*-(Phenyl)-*N*-[2-(4′-chlorophenylsulphonamido)-ethyl]nitrone (18d). Obtained as colourless amorphous solid, mp 149–151°C. (Found: C, 52.2, H, 4.45; N, 8.1, S, 9.7. $C_{15}H_{15}$ N_2O_3ClS requires: C, 53.2, H, 4.45; N, 8.25, S, 9.45 %). HRMS: 338.0493. $C_{15}H_{15}N_2O_3$ requires: 338.0492; δ: 8.1(d, 2H, *J*=8.1 Hz, Ar–H), 7.7(d, 2H, *J*=8.1 Hz, Ar–H), 7.35(m, 5H, Ar–H), 6.48 (br, 1H, HC═N), 4.1 (m, 2H, NCH_2N), 3.65 (br, 1H, NH) and 3.41(m, 2H, NCH_2N). *m/z*(%) 339 (M+1, 100), 323 (7), 218 (11), 149 (21), 91 (25), 69 (47), 57 (56) and 43 (40).

1.2.5. *C*-(4-Trifluoromethylphenyl)-*N*-[2-(4′-chlorophenylsulphonamido)ethyl]nitrone (18e). Obtained as colourless needles from ethyl acetate (590 mg, 58%), mp 171–172°C. (Found: C, 47.1; H, 3.6; N, 6.85; S, 7.8. $C_{16}H_{14}ClF_3N_2O_3S$ requires: C, 47.25; H, 3.45; N, 6.9; S, 7.95%); δ: 3.50 (q, *J*=5.4 Hz, 2H, CH_2NH), 4.10 (t, *J*=5.1 Hz, 2H, CH_2N^+), 5.92 (t, *J*=5.4 Hz,1H, NH), 7.45 (m, 3H, CH═N^++2ArH) and 7.70–8.20 (3×d, *J*=8.0 Hz, 3×2H, ArH). ν_{max} (film): 3100(br, CH), 1588(C═N), 1475, 1422, 1325, 1174, 1160, 1133, 1095, 861 and 765 cm^{-1}. *m/z(%)* 406 (M^+, <1), 186 (100), 175 (43), 159 (54) and 111 (68).

1.2.6. *C*-(4-Cyanophenyl)-*N*-[2-(4′-chlorophenylsulphonamido)ethyl]nitrone (18f). Obtained as colourless needles from ethyl acetate (309 mg, 34%), mp 149–151°C. (Found: C, 52.55; H, 4.05; N, 11.4; S, 8.95. $C_{16}H_{14}ClN_3O_3S$ requires: C, 52.8; H, 3.9; N, 11.55; S, 8.8%); δ: 3.49 (t, *J*=5.3 Hz, 2H, CH_2NH), 4.13 (t, *J*=5.0 Hz, 2H, CH_2N^+), 5.80 (t, *J*= 5.8 Hz,1H, NH), 7.45 (m, 3H, CH═N^++2ArH) and 7.70–8.25 (3×d, *J*=8.0 Hz, 3×2H, ArH). ν_{max} (film): 3250 (br, NH), 3084 (br, CH), 2228(C═N), 1587 (C═N), 1475, 1426, 1324, 1157, 1096, 1085, 830 and 754cm^{-1}. *m/z*(%) 363 (M^+, <1), 217 (11), 188 (27), 175 (55), 143 (100), 130 (27) and 111 (76).

1.2.7. *C*-(2-Phenylethenyl)-*N*-[2-(4′-chlorophenylsulphonamido)ethyl]nitrone (18g). Obtained as colourless needles from ethyl acetate [1.5 mmol scale (409 mg, 75%)], mp 186–188°C. (Found: C, 56.1; H, 4.9; N, 7.95. $C_{17}H_{17}ClN_2O_3S$ requires: C, 56.0; H, 4.7; N, 7.7%); δ (DMSO-d_6): 3.26 (t, *J*=5.3 Hz, 2H, CH_2NH), 3.48 (q, *J*= 5.5 Hz, 2H, CH_2N^+) and 7.30–8.40 (m, 12H, ArH). ν_{max} (film): 3000 (br, NH, CH), 1569 (C═N), 1473, 1410, 1326, 1162, 1132, 1094, 983,826 and 749 cm^{-1}. *m/z*(%) 364 (M^+, 2), 345 (8), 260 (25), 175 (60), 160 (20), 144 (75), 130 (42), and 111 (100).

1.2.8. *C*-(2-Pyrrolo)-*N*-[2-(4′-chlorophenylsulphonamido)-ethyl]nitrone (31). Obtained as colourless needles from ethyl acetate (433 mg, 53%), mp 164.5–166°C. (Found: C, 47.7; H, 4.35; N, 13.0, S, 9.65. $C_{13}H_{13}ClN_3O_3S$ requires: C, 47.8; H, 4.05; N, 12.9, S, 9.8%); δ: 3.37 (q, *J*=5.2 Hz, 2H, CH_2NH), 3.90 (t, *J*=4.9 Hz, 2H, CH_2N^+), 6.30, 6.46 and 6.97 (d, t, *J*=3.0 Hz, 3H, pyrrole H), 6.90 (t, *J*=6.0 Hz, 1H, NH), 7.45 and 7.85 (2×d, *J*=8.0 Hz, 2×2H, ArH), and 11.70 (br, 1H, pyrrole NH). ν_{max} (film): 3375 (br, NH), 3030 (br, CH), 2800 (br, NH), 1621 (C═N), 1585, 1476, 1423, 1328, 1158, 1094, 825 and 753 cm^{-1}. *m/z*(%)327 (M^+, 6), 244 (6), 175 (17), and 107 (100).

1.2.9. *C*-[2-(2′-Thienyl)ethenyl]-*N*-[2(-4′-chlorophenylsulphonamido)ethyl]nitrone (28b). Obtained as colourless needles from ethyl acetate (797 mg, 86%), mp 172–173°C. (Found: C, 48.5; H, 4.3; N, 7.5. $C_{15}H_{15}ClN_2O_3S_2$ requires: C, 48.6; H, 4.1; N, 7.6%); δ: 3.42 (t, *J*=5.1 Hz, 2H, CH_2NH), 3.94 (t, *J*=5.0 Hz, 2H, CH_2N^+), 6.61 (m, 1H, NH), 7.1–7.38 (m, 6H, 3×thiophene H, CH═CH═CH), 7.50 and 7.83 (2×d, *J*=8.5 Hz, ArH); ν_{max} (film): 3080 br, CH), 1602 (C═N), 1569, 1473, 1324, 1161, 1132, 1093, 967 and 752 cm^{-1}. *m/z*(%)370 (M^+, 16), 353 (12), 260 (43), 195 (19), 175 (57), 166 (43), 150 (91), 136 (38), 121 (34) and 111 (100).

1.2.10. *C*-(2-Thienyl)-*N*-[2-(4′-chlorophenylsulphonamido)ethyl]nitrone (28c). Obtained as colourless needles from ethyl acetate (604 mg, 70%)], mp 174–175.5°C. (Found: C, 45.15; H, 3.95; N, 7.85, S 18.5. $C_{13}H_{13}ClN_2O_3S_2$ requires: C, 45.3; H, 3.8; N, 8.1, S 18.6 %); δ: 3.47 (q, *J*=5.1 Hz, 2H, CH_2NH), 4.08 (t, *J*=5.1 Hz, 2H, CH_2N^+), 6.17(m, 1H, NH), 7.15 (m, 1H, CH═NO) and 7.7–7.8 (m, 7H, thiophene H and ArH). ν_{max} (film): 3050 (br,CH), 1586 (C═N), 1476, 1335, 1161, 1093, 828 and 758 cm^{-1}. *m/z*(%) 344 (M^+, 10), 174 (29), 169 (42), 152 (23), 124 (98) and 111 (100).

1.2.11. *C*-[2-(2′-Furyl)ethenyl]-*N*-[2-(4′-chlorophenylsulphonamido)ethyl]nitrone (28d). Obtained as colourless amorphous solid from ethyl acetate). [5 mmol scale (1.28 g, 72%)], mp 167–168°C. (Found: C, 51.10; H, 4.5; N, 7.7. $C_{15}H_{15}ClN_2O_4S$ requires: C, 50.8; H, 4.3; N, 7.9%); δ: 340 (t, *J*=5.0 Hz, 2H, CH_2NH), 3.94 (t, *J*=5.0 Hz, 2H, CH_2N^+), 6.46 (m, 1H, CH═*CH*═CH),6.59 (m, 1H, furyl H) and 7.45–7.9 (m, 8H, ArH, furyl H, and CH═N^+); ν_{max} (film): 3080 (br, CH), 2800 (br), 1619 (C═N), 1578, 1475, 1324, 1203, 1160, 1131, 1091, 931 and 738 cm^{-1}. *m/z*(%) 356 (M^+, 4), 354 (M^+, 11), 175 (33), 161 (14), 150 (14), 134 (100), 121 (37) and 111 (63).

1.2.12. *C*-(2-Furyl)ethenyl]-*N*-[2-4′-chlorophenylsulphonamido)ethyl]nitrone (28e). Obtained as colourless amorphous solid from ethyl acetate (460 mg, 56%)], mp 143.5–146°C. (Found: C, 47.3; H, 3.9; N, 8.45, S, 9.75. $C_{13}H_{13}ClN_2O_4S$ requires: C, 47.5; H, 4.0; N, 8.5, S, 9.75%); δ: 3.47 (q, *J*=5.4 Hz, 2H, CH_2NH), 4.02 (t, *J*= 5.1 Hz, 2H, CH_2N^+), 6.07 (t, *J*=5.7 Hz, 1H, NH), 6.57 (m, 1H, furyl H) and 7.45–7.9 (m, 8H, ArH, furyl H, and CH═N^+); ν_{max} (film): 3080 (br, CH), 2800(br), 1586 (C═N), 1478, 1332, 1225, 1158, 1085, 824 and 775 cm^{-1}. *m/z*(%) 330 (M^+, 2), 328 (M^+, 6), 175 (24), 153 (20), 125 (20) and 108 (100).

1.3. General procedure for the 1,3-dipolar cycloaddition of nitrones

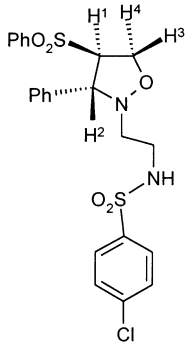
The nitrone (0.3 mmol) was taken up in dry xylene (20 ml) and the dipolarophile (0.33 mmol) added. The mixture was heated to 120°C for 16 h, cooled and xylene removed under reduced pressure. The residue was purified by column chromatography on kieselgel, eluting with 1:1 v/v petroleum ether–ethyl acetate, followed by crystallisation from

petroleum ether–ethyl acetate. Products usually comprised a 1:1 mixture of *endo*- and *exo*-isomers.

1.3.1. Cycloadduct (4). Obtained as a single *endo*-stereoisomer [0.3 mmol scale (97 mg, 64%)] as colourless needles from ether, mp 163–165°C. (Found: C, 54.4, H, 4.65; N, 5.45. $C_{23}H_{24}ClN_2O_5S_2$ requires: Found: C, 54.5, H, 4.55; N, 5.55%); δ: 2.6 and 2.8 (2×m, 2H, CH_2-isoxazolidine) 3,05–3.2 (2×m, 2H, CH_2NHSO_2PhCl), 3.97 (d, J=8.0 Hz, 1H, H^2), 4.01(m, 1H, H^1), 4.15 (t, J=9.0 Hz, 1H, H^4), 4.45 (dd, J=3.0 and 10.0 Hz, 1H, H^3), 5.1 (t, J=5.5 Hz, 1H, NH) and 7.0–7.8 (m, 9H, ArH), ν_{max} (film): 3250 (br, NH), 2900 (br, CH), 1787 (w, imide), 1707 (s, C=O, imide), 1611, 151 3, 1436, 1330, 12 52, 1163, 1086, 829 and 736 cm^{-1}. *m/z*(%) 507(M^+, <1), 365 (5), 302 (100), 245 (51), 175 (23), 160 (19), 141 (14), 118 (71) and 91(55).

Enhancement (%)

Irradiated hydrogen	H^1	H^2	H^3	H^4
H^1				4.4
H^2				
H^3				24
H^4	8.7		31	

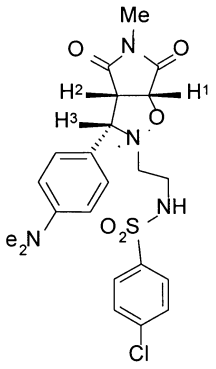


1.3.2. Cycloadduct (19a). Obtained as a 1:1 mixture [1.40 mmol scale (560 mg, 81% combined yield)] of separable *endo*- and *exo*-isomers.

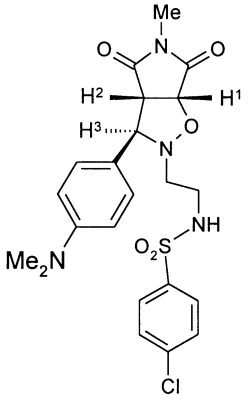
exo-Isomer: Colourless amorphous solid from ethyl acetate–hexane, mp 202–204°C. (Found: C, 53.7; H, 5.1; N, 11.5, S, 6.4. $C_{22}H_{25}ClN_4O_5S$ requires: C, 53.65; H, 5.1; N, 11.35, S, 6.5%); δ: 2.65 and 2.9 (2×m, 2H, CH_2NO), 2.95, (s, 6H, NMe_2), 3,03 (s, 3H, NMe), 3.02–3.2 (m, 2H, CH_2NH), 3.6 (dd, J=8.5 and 7.5 Hz, 1H, H^2), 3.88 (d, J=8.5 Hz, 1H, H^3), 4.87 (d, J=7.5 Hz, 1H, H^1), 5.16 (t, J=5.8 Hz, 1H, NH) and 6.55–7.80 (4×d, J=8.6 Hz, 4×2H, ArH), ν_{max} (film): 3250 (br, NH), 2900 (br, CH), 1786 (w, imide), 1706 (s, C=O), 1612, 1525, 1425, 1435, 1329, 1285, 1164, 1086, 820 and 752 cm^{-1}. *m/z*(%) (FAB) 495 (M+1, 33), 493 (M+1, 100), 381 (21) and 288 (51).

Enhancement (%)

Irradiated hydrogen	H^1	H^2	H^3
H^1		9.5	
H^2	16.9		8.9
H^3		11.4	



endo-Isomer: Colourless needles from ethyl acetate–hexane, mp 189–191°C. (Found: C, 53.45; H, 4.95; N, 11.6, S, 6.4. $C_{20}H_{19}ClN_3O_5S$ requires: C, 53.6; H, 5.1; N, 11.35, S, 6.5%); δ: (300 MHz, 50°C), 2.55 (m, 2H, CH_2NO) 2.95 (s, 6H, NMe_2), 3,03 (s, 3H, NMe), 3.08 (m, 2H, CH_2NH), 3.63 (dd, J=2.8 and 7.1 Hz, 1H, H^2), 4.05 [broad peak at 20°C (50°C, d, J=2.8 Hz, 1H, H^3)], 4.86 (d, J=7.1 Hz, 1H, H^1), 4.90 (t, J=5.3 Hz, 1H, NH) and 6.60–7.80 (4×d, J=8.6 Hz, 4×2H, ArH),. *m/z*(%) (FAB) 495 (M+1, 33), 493 (M+1, 100), 381 (18) and 288 (44).

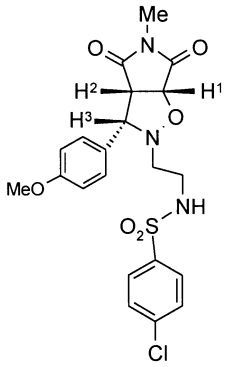


1.3.3. Cycloadduct (19b). Obtained as a 1:1 mixture [1.28 mmol scale (560 mg, 91% combined yield)] of separable *endo*- and *exo*-isomers.

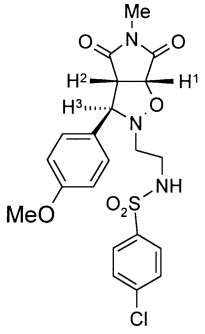
exo-Isomer: Colourless prisms from ethyl acetate–hexane, mp 185–186°C. (Found: C, 52.5, H, 4.7; N, 8.65, S, 6.85. $C_{21}H_{22}ClN_3O_6S$ requires: C, 52.55; H, 4.6; N, 8.75, S, 6.7%); δ: 2.68 and 2.88 (2×m, 2H, CH_2NO) 3.02, (s, 3H, NMe), 3,05–3.3 (m, 2H, CH_2NH), 3.65 (t, J=8.0 Hz, 1H, H^2), 3.80 (s. 3H, OMe), 3.91 (d, J=8.8Hz, 1H, H^3), 4.89 (d, J=7.3 Hz, 1H, H^1), 5.15 (t, J=6.0 Hz, 1H, NH) and 6.80–7.85 (4×d, J=8.7 Hz, 4×2H, ArH), ν_{max} (film): 3250 (br, NH), 2900 (br, CH), 1787 (w, imide), 1707 (s, C=O, imide), 1611, 151 3, 1436, 1330, 12 52, 1163, 1086, 829 and 736 cm^{-1}. *m/z*(%) 481/479 (M^+, <1), 275 (10), 175 (22), 148 (100), 121 (81) and 111 (49).

Enhancement (%)

Irradiated hydrogen	H^1	H^2	H^3
H^1		9.5	
H^2	18.9		12.71
H^3		12.1	



endo-Isomer: Colourless amorphous solid from ethyl acetate–hexane, mp 153–154°C. (Found: C, 52.65, H, 4.85; N, 8.45, S, 6.75. $C_{21}H_{22}ClN_3O_6S$ requires: C, 52.55; H, 4.6; N, 8.75, S, 6.7%); δ: 2.4 and 2.58 (2×m, 2H, CH_2NO), 3.08 (m, 5H, NMe+CH_2NH), 3.63 (dd, J=3.0 and 7.3 Hz, 1H, H^2), 3.82 (s. 3H, OMe), 4.1 (d, J=3.0 Hz, 1H, H^3), 4.91 (d, J=7.3 Hz, 1H, H^1), 5.17 (t, J=6.0 Hz, 1H, NH) and 6.80–7.80 (4×d, J=8.7 Hz, 4×2H, ArH). *m/z*(%) 481/479 (M^+, <1), 275 (10), 175 (22), 148 (100), 121 (77) and 111 (66).

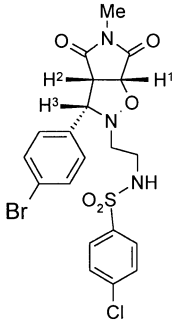


1.3.4. Cycloadduct (19c). Obtained as a 1:1 mixture [1.44 mmol scale (592 mg, 69% overall)] of separable *endo*- and *exo*-isomers.

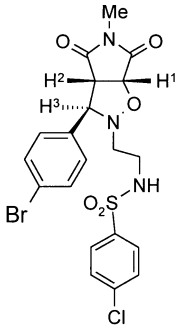
exo-Isomer: Colourless needles from ethyl acetate–hexane, mp 178–181°C. (Found: C, 46.65, H, 3.65; N, 8.05, S, 6.15. $C_{20}H_{19}BrClN_3O_5S$ requires: C, 45.45, H, 3.6; N, 7.95, S, 6.05%); δ: (400 MHz), 2.7 and 2.87 (2×m, 2H, CH_2NO), 3.01 (s, 3H, NMe), 3.1 and 3.2(2×m, 2H, CH_2NH), 3.71 (t, J=8.0 Hz, 1H, H^2), 3.93 (d, J=8.7 Hz, 1H, H^3), 4.91 (d, J=7.3 Hz, 1H, H^1), 5.15 (br, 1H, NH) and 7.0–7.85 (4×d, J=8.6 Hz, 4×2H, ArH), ν_{max} (film): 3278 (br, NH), 2900 (br, CH), 1790 (w, imide), 1705 (s, C=O, imide), 1331, 1280 11671095, 827 and 751 cm^{-1}. *m/z*(%) (FAB) 529 (M^+, 100), 527 (M^+, 75), and 323 (59).

Enhancement (%)

Irradiated hydrogen	H^1	H^2	H^3
H^1		5.6	
H^2	12.6		9.7
H^3		6.5	



endo-Isomer: colourless amorphous solid from ethyl acetate–hexane, mp 186–187°C. (Found: C, 45.7, H, 3.6; N, 7.7, S, 6.25. $C_{20}H_{19}BrClN_3O_5S$ requires: C, 45.45, H, 3.6; N, 7.95, S, 6.05%); δ: (50°C): 2.5 and 2.63 (2×m, 2H, CH_2NO), 3.5 (s, 3H, NMe), 3.12 (m, 2H, CH_2NH), [broad peak at 20°C, 3.63 (50°C dd, J=3.1 and 7.6 Hz, 1H, H^2)], 4.12 (d, J=3.1 Hz, 1H, H^3), 5.01 (d, J=7.5 Hz, 1H, H^1), 5.1 (br, 1H, NH) and 6.80–7.80 (4×d, J=8.7 Hz, 4×2H, ArH), *m/z*(%) (FAB) 529 (M^+, 100), 527 (M^+, 75), and 323 (53).

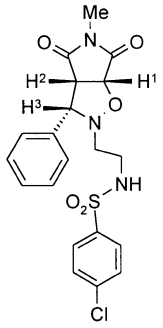


1.3.5. Cycloadduct (19d). A solution of nitrone (**18d**) (0.17 g, 0.5 mmol) and NMM (0.08 g, 1.2 equiv.) in degassed xylene was boiled under reflux under a nitrogen atmosphere for 18 h. After cooling the solvent was removed in vacuo and the residue, which comprised a 1:1 mixture of *endo*- and *exo*-isomers, was subjected to column chromatography on silica eluting with 1:9 v/v ethyl acetate–hexane to afford the *endo*- and *exo*-isomers (0.18 g, 79 % combined yield).

exo-Isomer: Colourless prisms from petroleum ether–ether, mp 196–198°C.(Found: C, 53.05, H, 4.5, N, 9.6. $C_{20}H_{20}N_3O_5ClS$ requires: C, 53.5, H, 4.5, N, 9.35 %.); δ (400 MHz): 7.82 (d, 2H, Ar–H), 7.51 (d, 2H, Ar–H), 7.35 (m, 3H, Ar–H), 7.11 (m, 2H, Ar–H), 5.11 (br, 1H, NH), 4.90 (d, 1H, J=7.24 Hz, H^1), 3.97 (d, 1H, J=8.7 Hz, H^3), 3.70 (t, 1H, J=8.0 Hz, H^2), 3.22 and 3.11 (2×m 2H, $SNCH_2$), 3.0 (s, 3H, NMe), 2.91 and 2.70 (2×m, 2H, $ONCH_2$). *m/z*(%) (FAB) 450 (M+1, 100), 245 (51), 176 (11), 71 (13), 57 (15) and 43 (10).

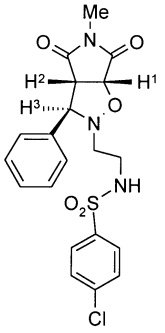
Enhancement (%)

Irradiated hydrogen	H^1	H^2	H^3
H^1		4.3	
H^2	5.2		6.5
H^3		5.7	



endo-Isomer: Colourless plates from petroleum ether–ether mp. 177–179°C. (Found: C, 53.95, H, 4.5; N, 9.35, Cl, 7.9. $C_{20}H_{20}N_3O_5ClS$ requires: C, 53.5, H, 4.5; N, 9.35, Cl, 7.9%); δ (400 MHz): 7.81(d, 2H, Ar–H), 7.5 (d, 2H, Ar–H), 7.4 (m, 3H, Ar–H), 7.3 (m, 2H, Ar–H), 5.13 (t, 1H, J=6.0 Hz, NH), 4.91 (d, 1H, J=7.3 Hz, H^1), 3.68 (dd, 1H, J=7.4 and 3.1 Hz, H^2), 3.1 (s, 3H, NMe), 3.2–3.1 (m, 3H, H^3 and NCH_2) and 2.6–2.5 (2m, 2H, NCH_2). *m/z*(%)

(FAB) 450 (M+1, 63), 413 (25), 391 (50), 245 (60), 149 (100) and 43 (52).

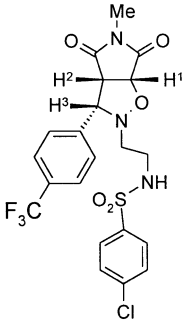


1.3.6. Cycloadduct (19e). Obtained as a 1:1 mixture [1.40 mmol scale (667 mg, 92% combined yield)] of separable *endo*- and *exo*-isomers.

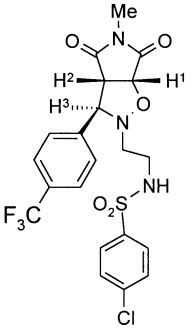
exo-Isomer: Colourless prisms from ethyl acetate–hexane, mp 187–189°C. (Found: C, 48.8, H, 3.9; N, 7.85, S, 6.4. $C_{21}H_{19}Cl\ F_3N_3O_5S$ requires: C, 48.7, H, 3.7; N, 8.1, S, 6.2%); δ: (400 MHz), 2.7 and 2.9 (2×m, 2H, CH_2NO), 3.1 (s, 3H, NMe), 3.2 (m, 2H, CH_2NH), 3.75 (t, J=8.0 Hz, 1H, H^2), 4.03 (d, J=8.6 Hz, 1H, H^3), 4.9 (d, J=7.3 Hz, 1H, H^1), 5.15 (t, J=5.1 Hz, 1H, NH) and 7.2–7.8 (4×d, J=8.6 Hz, 4×2H, ArH), ν_{max} (film): 3280 (br, NH), 2900 (br, CH), 1788 (imide), 1708 (C=O, imide), 1620, 1586, 1436, 1324, 1288, 1164, 1068, 830 and 738 cm^{-1}. *m/z*(%) (FAB) 519 (M^+, 32), 517 (M^+, 97) and 313 (100).

Enhancement (%)

Irradiated hydrogen	H^1	H^2	H^3
H^1		8.5	
H^2	14.8		9.7
H^3		10.9	



endo-Isomer: Colourless prisms from ethyl acetate–hexane, mp 157–158°C. (Found: C, 48.7, H, 3.85; N, 8.0, S, 6.25. $C_{21}H_{19}Cl\ F_3N_3O_5S$ requires: C, 48.7, H, 3.7; N, 8.1, S, 6.2 %). δ (300 MHz, 50°C) 2.57 and 2.7 (2×m, 2H, CH_2NO), 3.07(s, 3H, NMe), 3.12 (m, 2H, CH_2NH), [broad peak at 20°C, 3.65 (50°C, dd, J=3.5 and 7.4 Hz, 1H, H^2), 4.22 (d, J=3.2 Hz, 1H, H^3), 4.88 (d, J=7.3 Hz, 1H, H^1), 5.05 (br, 1H, NH) and 7.2–7.80 (4×d, J=8.6 Hz, 4×2H, ArH). *m/z*(%) (FAB): 519 (M^+, 22), 517 (M^+, 67) and 313 (100).

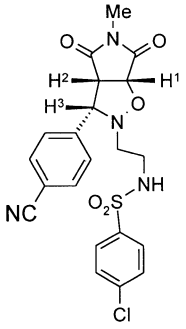


1.3.7. Cycloadduct (19f). Obtained as a 1:1 mixture [0.5 mmol scale (198 mg, 80% combined yield)] of separable *endo*- and *exo*-isomers.

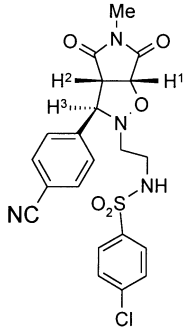
exo-Isomer: Colourless amorphous solid from ethyl acetate–hexane, mp 138–140°C. (Found: C, 53.15, H, 4.3; N, 11.6, S, 6.7.4. $C_{21}H_{19}ClN_4O_5S$ requires: C, 53.1, H, 4.05; N, 11.8, S, 6.75 %), δ: 2.75 and 2.93 (2×m, br, 2H, CH_2NO), 2.98 (s, 3H, NMe), 3.16 (m, 2H, CH_2NH), 3.77 (t, J=8.0 Hz, 1H, H^2), 4.03 (d, J=8.7 Hz, 1H, H^3), 4.93 (d, J=7.3 Hz, 1H, H^1), 5.25 (t, J=6.0 Hz, 1H, NH) and 7.3–7.8 (4×d, J=8.3 Hz, 4×2H, ArH), ν_{max} (film): 3250 (br, NH), 2900 (br, CH), 2230 (CN), 1788 (imide), 1707 (C=O, imide), 1587, 1435, 1331, 1283, 1163, 1086, 831 and 735 cm^{-1}. *m/z*(%) (FAB): 477 (M+1, 33), 475 (M+1, 100) and 270 (59).

Enhancement (%)

Irradiated hydrogen	H^1	H^2	H^3
H^1		8.3	
H^2	18.7		12.4
H^3		8.8	



endo-Isomer: Colourless amorphous solid from ethyl acetate–hexane, mp 182–184°C. (Found: C, 53.15, H, 4.0; N, 11.65, S, 6.75. $C_{21}H_{19}ClN_4O_5S$ requires: C, 53.1, H, 4.05; N, 11.8, S, 6.75 %). δ (300 MHz) 2.5 and 2.65 (2×m, br, 2H, CH_2NO), 3.07 (m, 5H, NMe+CH_2NH), 3.65 (dd, J=3.2 and 7.2 Hz, 1H, H^2), 4.2 [broad peak at 20°C, (50°C, d, J= 3.2 Hz, 1H, H^3), 4.95 (d, J=7.3 Hz, 1H, H^1), 5.09 (t, J= 6.0 Hz 1H, NH) and 7.4–7.8 (4×d, J=8.6 Hz, 4×2H, ArH), *m/z*(%) (FAB) 477 (M+1, 33), 475 (M+1, 100) and 270 (95).



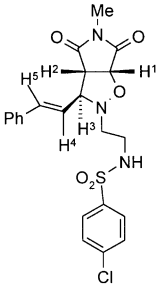
1.3.8. Cycloadduct (19g). Obtained as a 1:1 mixture [0.3 mmol scale (73 mg, 57% combined yield)] of separable *endo*- and *exo*-isomers.

exo-Isomer: Colourless amorphous solid from ethyl acetate–hexane, mp 96–98°C. (Found: C, 55.4, H, 4.8; N, 8.6,. $C_{22}H_{22}ClN_3O_5S$ requires: C, 55.5, H, 4.7; N, 8.8%), δ: 2.7 (m, br, 1H, C*H*HNO), 3.09 (σ, 3H, Nme), 3.0–3.2 (m, 3H, CH_2NH, C*H*HNO), 3.47 (t, J=8.5 Hz, 1H, H^3), 3.61 (t, J=7.7 Hz, 1H, H^2), 4.84 (d, J=7.4 Hz, 1H, H^1), 5.13 (t, J=5.1 Hz, 1H, NH), 5.79 (dd, J=15.8 and 9.2 Hz, 1H, H^2),

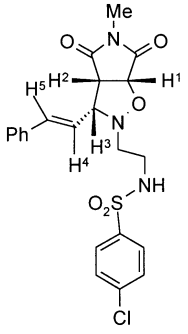
6.66 (d, J=15.8 Hz, 1H, H^5) and 7.35–7.8 (m, 9H, ArH), ν_{max} (film): 3300 (br, NH), 2900 (br, CH), 1786 (w, imide), 1705 (s, C=O, imide), 1586, 1432, 1332, 1284, 1165, 1095 and 752 cm^{-1}. *m/z*(%) 175 (25), 144 (73), 130 (20) and 111 (100).

Enhancement (%)

Irradiated hydrogen	H^1	H^2	H^3	H^4	H^5
H^1		12.9			
H^2	16.9				
H^3	5.8	6.0		3.1	12.3
H^4					13.7



endo-Isomer: Colourless amorphous solid from ethyl acetate–hexane, mp 174.5–176°C. (Found: C, 55.45, H, 4.85; N, 8.85 $C_{22}H_{22}ClN_3O_5S$ requires C, 55.5, H, 47; N, 8.8%); δ: 2.8 and 2.9 (m, br, 2H, CH_2NO), 3.05 (σ, 3H, NMe), 3.1 (m, 2H, CH_2NH), 3.47 (d, J=7.1 Hz, 1H, H^2), 3.9 (m, br, 1H, H^3), [note: becomes a doublet at 50°C, 4.83 (d, J=7.3 Hz, 1H, H^1), 5.13 (t, J=6.0 Hz, 1H, NH), 6.15 (dd, J=15.8 and 7.1 Hz, 1H, H^4), 6.63 (d, J=15.8 Hz, 1H, H^5) and 7.16–7.9 (m, 9H, ArH), *m/z*(%) 175 (40), 160 (35), 144 (83), 130 (25) and 111 (100).



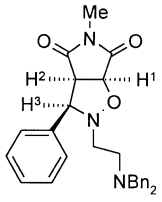
1.4. Compounds (14)–(16)

anti-Benzaldoxime (0.13 g, 1 mmol) was added to a stirred, ice-cold suspension of NaH (60% oil dispersion; 90 mg, 2.2 mmol) in DMF (5 ml), followed immediately by addition of 2-chloro-*N*,*N*-dibenzylaminoethane hydrochloride (0.33 g, 1.1 mmol). After 1 h, LiI (30 mg) was added and stirring continued for 4 h at 20°C, Heating at 90°C for a further 1 h was required to complete the reaction based on TLC evidence. Water (20 ml) was then added and the mixture extracted with DCM (5×25 ml). The combined organic layer was dried ($MgSO_4$), the solvent removed under reduced pressure, the residue taken up in degassed xylene and NMM (0.11 g, 0.99 mmol) added. The mixture was boiled under reflux under a nitrogen atmosphere for 18 h. Removal of xylene under reduced pressure gave a pale yellow solid which consisted of a 2:1 mixture of (**15**) and (**16**). Flash chromatography (SiO_2) of the this solid eluting with 9:1 v/v ether–petroleum ether afforded cycloadducts (**15**) and (**16**) in 53% combined yield.

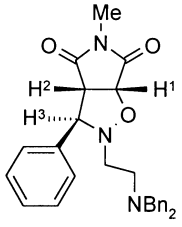
1.4.1. Cycloadduct (15). Obtained (28%) as a colourless amorphous solid, mp 149–151°C. (Found: C, 73.5, H, 6.7, N 9.15. $C_{28}H_{29}N_3O_3$ required: C, 73.8; H, 6.4; N, 9.2%); δ (400 MHz): 7.4–7.1 (m, 15H, Ar–H), 4.87 (d, 1H, J=7.3 Hz, H^1), 3.93 (d, 1H, J=8.6 Hz, H_3), 3.68 (t, 1H, J=8.0 Hz, H_2), 3.75 (m, 4H, CH_2), 2.92 (s, 3H, NMe) and 2.81–2.62 (m, 4H, CH_2); *m/z*(%) (FAB) 456 (M+1, 26), 364 (12), 226 (49), 210 (70), 91 (100) and 55 (23).

Enhancement (%)

Irradiated hydrogen	H^1	H^2	H^3
H^1		9.2	
H^2	11.9		4.2
H^3		4.7	



1.4.2. Cycloadduct (16). Obtained (25%) as a pale yellow thick oil. (HRMS: 455.2203. $C_{28}H_{29}N_3O_3$ requires: 455.2208). δ (400 MHz) (C_6D_6): 7.6–7.0 (m, 15H, Ar–H), 4.18 (d, 1H, J=7.4 Hz, H_1), 3.52 (s, 2H, CH_2), 3.42 (d, 1H, J=5.6 Hz, H_3), 3.4–3.2 (m, 2H, CH_2), 3.35 (s, 3H, NMe), 2.9 and 2.89 (dd, 1H, J=3.2 and 7.3 Hz, H_2), 2.59 (s, 2H, CH_2) and 2.37 (m, 2H, CH_2); *m/z* (FAB) 456 (M+1, 18), 364 (9), 240 (27), 210 (91) and 91 (100).



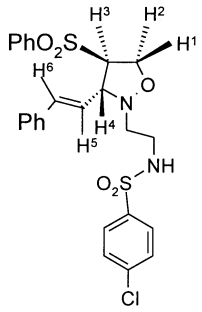
1.5. Cycloadducts (24)–(26)

Obtained as a 5:1:1 mixture of isomers which were separated by column chromatography eluting with 10:1 v/v toluene–EtOAc. [2 mmol scale (710 mg, 64% combined yield)]

1.5.1. Cycloadduct (24). Obtained as a colourless amorphous solid from toluene–ethyl acetate (497 mg, 47%), mp 54.5–55.5°C. (Found: C, 56.4, H, 5.0; N, 5.0. $C_{25}H_{225}ClN_2O_5S_2$ requires: Found: C, 56.3, H, 4.7; N, 5.2%); δ: 2.75 and 2.85 (2×m, 2H, CH_2NO), 3.10 (m, 2H, CH_2NH), 3. 5 (t, J=7.5 Hz, 1H, H^4), 3.85 (m, 1H, H^3). 3.85 (m, 1H, H^3), 4.0 (dd, J=8 and 10 Hz, 1H, H^1), 4.4 (dd, J=3.5 and 10 Hz, 1H, H^2) 5.7 (dd, J=8.5 and 16 Hz, 1H, H^5), 6.1 (d, J=16 Hz, 1H, H^6) and 7.0–8.0 (m, 14H, ArH), *m/z*(%) 411 (1), 347 (6), 284 (3), 213 (3), 175 (27), 144 (100), and 115 (70).

Enhancement (%)

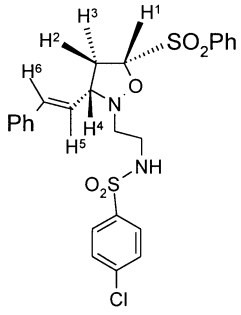
Irradiated hydrogen	H^1	H^2	H^3	H^4	H^5	H^6
H^1		30.8	13.3			
H^2	23.1		0.85			
H^3	6.5				9.3	
H^4					13.7	4.6



1.5.2. Cycloadduct (25). Obtained as colourless amorphous solid from toluene–ethyl acetate (102 mg, 10%); δ: 2.65 (m, 1H, CHHNO), 2.86 (t, J=9.2 Hz, 2H, H^2 and H^3) 2.93 (m, 1H, C*H*HNO), 3.16 (m, 2H, CH_2NH), 3.34 (m, 1H, H^4), 4.9 (t, J=7.1 Hz, 1H, H^1), 5.44 (t, J=5.1 Hz, 1H, NH), 5.88 (dd, J=16.0 and 8.6 Hz, 1H, H^5), 6.53 (d, J=16.0 Hz, 1H, H^6) and 7.1–7.95 (m, 9H, ArH), *m/z*(%) 361 (15), 175 (15), 144 (45), 125 (25), 115 (40) and 77 (54).

Enhancement (%)

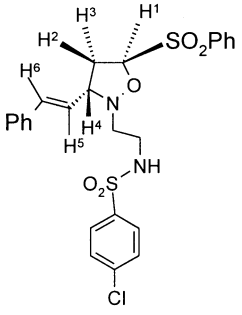
Irradiated hydrogen	H^1	H^2 H^3	H^4	H^5	H^6
H^1		8.7			
H^2 H^3	4.4		5.0	8.1	5.8
H^4		5.1		2.2	14.5



1.5.3. Cycloadduct (26). Obtained as colourless amorphous solid from toluene–ethyl acetate (111 mg, 10%), δ: 2.63 (m, 1H, H^2), 3.05 (m, 5H, ONCH_2CH_2NH and H^3), 3.8 (m, 1H, H^4), 4.89 (m, 1H, H^1), 5.17 (s, br, 1H, NH), 5.9 (dd, J=16.0 and 9.3 Hz, 1H, H^5), 6.56 (d, J=16.0 Hz, 1H, H^6) and 7.2–7.95 (m, 9H, ArH), *m/z*(%) 361 (15), 175 (25), 144 (48), 125 (44), 115 (49) and 77 (100).

Enhancement (%)

Irradiated hydrogen	H^1	H^2	H^3	H^4	H^5	H^6
H^1			8.6			
H^2			9.2			
H^3	19.3	20.7			8.1	1.8
H^4		13.7			3.3	14.3

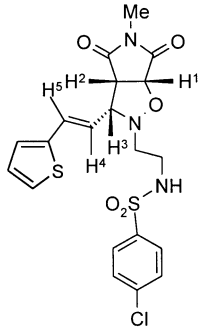


1.5.4. Cycloadducts (29b) and (30b). Obtained as a 1:1 mixture [2.24 mmol scale (881 mg, 82% combined yield)] of separable *endo*- and *exo*-isomers.

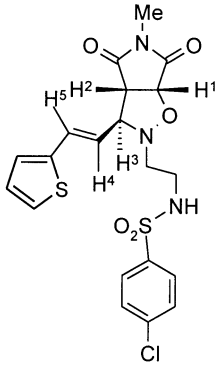
exo-Isomer (**29b**): Colourless cubes from ethyl acetate–hexane, mp 179–181°C. (Found: C, 50.0, H, 4.25; N, 8.55. $C_{20}H_{20}ClN_3O_6S$ requires: C, 49.85, H, 4.2; N, 8.7%); δ: 2.65 (m, br, 1H, C*H*HNO), 3.09 (s, 3H, Nme), 3.0–3.25 (m, 3H, CH_2NH and C*H*HNO), 3.43 (t, J=8.6 Hz, 1H, H^3), 3.6 (t, J=7.6 Hz, 1H, H^2), 4.83 (d, J=7.3 Hz, 1H, H^1), 5.15 (t, J=5.9 Hz, 1H, NH), 5.6 (dd, J=15.6 and 9.3 Hz, 1H, H^4), 6.6 (d, J=15.5 Hz, 1H, H^5), 7.0 and 7.25 (2×m, 3H, thienyl H) and 7.45 and 7.8 (2×d, 4H, J=8.8 Hz, ArH), ν_{max} (film): 3300 (NH), 2900 (CH), 1786 (imide), 1705 (C=O imide), 1586, 1435, 1332, 1286, 1163, 1094, 961, 829 and 735 cm^{-1}. *m/z*(%) 370 (6), 262 (12), 195 (11), 175 (32), 150 (81), 136 (24), 121 (26) and 111 (100).

Enhancement (%)

Irradiated hydrogen	H^1	H^2	H^3	H^4	H^5
H^1		9.7			
H^2	16.9		5.4	3.3	
H^3		11.6		5.9	13.2



endo-Isomer (**30b**): Colourless amorphous solid from ethyl acetate–hexane, mp 165.5–167.5°C. (Found: C, 49.85, H, 4.35; N, 8.4. $C_{20}H_{20}ClN_3O_6S$ requires: C, 49.85, H, 4.20; N, 8.7%); δ: 2.76 and 2.9 (2×m, 2H, CH_2NO), 3.04 (s, 3H, NMe), 3.1(m, 2H, CH_2NH), 3.48 (d, J=6.7 Hz, 1H, H^2), 3.9 (m, 1H, H^3) [at 50°C becomes a doublet J=8.0 Hz], 4.82 (d, J=7.2 Hz, 1H, H^1), 5.1 (br, 1H, NH), 5.93 (dd, J=15.4 and 9.8 Hz, 1H, H^4), 6.74 (d, J=15.7 Hz, 1H, H^5), 7.0 and 7.2 (2×m, 2H, thiophene H), 7.45 and 7.8 (2×d, 4H, J=8.5 Hz, ArH), *m/z*(%) 353 (7), 260 (16), 175 (33), 166 (21), 150 (76), 136 (26), 121 (22) and 111 (100).



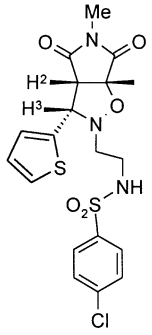
1.5.5. Cycloadduct (29c) and (30c). Obtained as a 1:1

mixture [1.16 mmol scale (460 mg, 68% combined yield)] of separable *endo*- and *exo*-isomers.

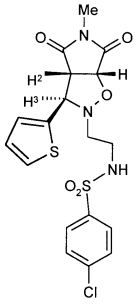
exo-Isomer (**29c**): Colourless prisms from ethyl acetate–hexane, mp 177–178°C. (Found: C, 47.2, H, 4.1, N, 9.15, S, 13.95. $C_{18}H_{18}ClN_3O_5S_2$ requires: C, 47.4, H, 4.0; N, 9.2, S, 14.05%), δ: 2.77 and 2.98 (2×m, 2H, CH_2NO), 3.02 (s, 3H, NMe), 3.2 (m, 2H, CH_2NH), 3.71 (t, J=8.3 Hz, 1H, H^2), 4.33 (d, J=9.2 Hz, 1H, H^3), 4.93 (d, J=7.2 Hz, 1H, H^1), 5.1 (br, 1H, NH), and 7.01–7.83 (m, 7H, ArH+thiophene H), ν_{max} (film): 3300 (NH), 2900 (CH), 1788 (imide), 1707 (C=O imide), 1586, 1436, 1331, 1286, 1163, 1086, 831 and 735 cm^{-1}., *m/z*(%) 344 (12), 251 (33), 175 (27), 124 (86) and 111 (100).

Enhancement (%)

Irradiated hydrogen	H^1	H^2	H^3
H^1		10	
H^2	19.9		17.8
H^3		14.6	



endo-Isomer (**30c**): Colourless amorphous solid from ethyl acetate–hexane, mp 160–163°C. (Found: C, 47.2, H, 4.2; N, 8.95, S, 13.85. $C_{18}H_{18}ClN_3O_5S_2$ requires: C, 47.4, H, 4.0; N, 9.2, S, 14.05%), δ: 2.5 and 2.65 (2×m, 2H, CH_2NO), 3.08 (m, 5H, NMe+CH_2NH), 3.65 (d, J=7.6 Hz, 1H, H^2), 4.70 [broad peak at 20°C, (50°C, s, 1H, H^3)], 4.9 (d, J=7.7 Hz, 2H, H^1+NH) and 6.9–7.8 (m, 7H, ArH+ thiophene H), *m/z*(%) 251 (14), 175 (28), 124 (84) and 111 (100).

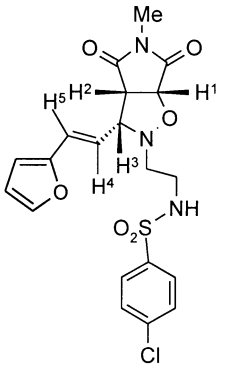


1.5.6. Cycloadducts (29d) and (30d). Obtained as a 1:1 mixture [2.8 mmol scale (1.02 g, 78% combined yield)] of separable *endo*- and *exo*-isomers.

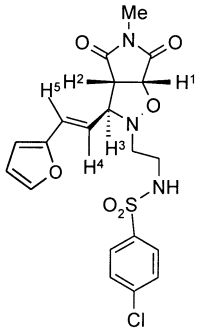
exo-Isomer (**29d**): Colourless cubes from ethyl acetate–hexane, mp 142–144°C. (Found: C, 51.6, H, 4.25, N, 8.95. $C_{20}H_{20}ClN_3O_6S$ requires:: C, 51.6, H, 4.3; N, 9.0%), δ: (400 MHz), 2.62 (m, 1H, C*H*HNO), 3.06 (s, 3H, NMe), 2.9–3.2 (m, 3H, CH_2NH, C*H*HNO), 3.39 (t, J=8.7 Hz, 1H, H^3), 3.57 (t, J=7.7 Hz, 1H, H^2), 4.82 (d, J=7.3 Hz, 1H, H^1), 5.21 (t, J=5.3 Hz, 1H, NH), 5.68 (dd, J=15.7 and 9.5 Hz, 1H, H^4), [6.3 (d, J=3.3 Hz, 1H), 6.37 (dd, J=3.3 and 1.8 Hz, 1H), 7.37 (d, J=1.6 Hz, 1H, furyl H), 6.4 (d, J=15.7 Hz, 1H, H^5) and 7.45 and 7.8 (2×d, J=8.8 Hz, 4H, ArH), ν_{max} (film): 3300 (NH), 2900 (CH), 1786 (imide), 1705 (C=O imide), 1436, 1331, 1287, 1163, 1094, 963, 829, and 736 cm^{-1}. *m/z*(%) 175 (33), 161 (29), 134 (91) and 111 (100).

Enhancement (%)

Irradiated hydrogen	H^1	H^2	H^3	H^4	H^5
H^1		7.9			
H^2	14.9		5.6	1.3	
H^3		10.7		5.0	13.0



endo-Isomer (**30d**): Colourless cubes from ethyl acetate–hexane, mp 156–158°C. (Found: C, 51.7, H, 4.4; N, 9.0. $C_{20}H_{20}ClN_3O_6S$ requires: C, 51.6, H, 4.3; N, 9.0%); δ: 2.75 and 2.9 (2×m, 2H, CH_2NO), 3.05 (s, 3H, NMe) 3.10 (m, 2H, CH_2NH), 3.47 (d, J=7.7 Hz, 1H, H^2), 3.9 (m, 1H, H^3), [at 50°C becomes a doublet J=8.0 Hz], 4.82 (d, J=7.3 Hz, 1H, H^1), 5.01 (t, J=5.8 Hz, 1H, NH), 6.06 (dd, J=15.8 and 8.5 Hz, 1H, H^4), 6.35 (m, 3H, H^5 and furyl H), 7.38 (s, 1H, furyl H) and 7.48–7.78 (2×d, 2×2H, J=8.4 Hz, ArH), *m/z*(%) 354 (4), 338 (6), 175 (30), 161 (22), 134 (100) and 111 (92).



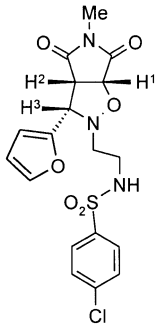
1.5.7. Cycloadducts (29e) and (30e). Obtained as a 2:1 mixture [0.95 mmol scale (309 mg, 74% combined yield)] of separable *endo*- and *exo*-isomers.

exo-Isomer (**29e**): Colourless needles from ethyl acetate–hexane, mp 170–171°C. (Found: C, 49.15, H, 4.05, N, 9.45, S, 7.35. $C_{18}H_{18}ClN_3O_6S$ requires: C, 49.15, H, 4.1; N, 9.55, S, 7.3%); δ: (400 MHz), 2.75 and 2.9 (2×m, 2H, CH_2NO), 3.04 (s, 3H, NMe) 3.15 (m, 2H, CH_2NH), 3.68 (t, J=8.0 Hz, 1H, H^2), 4.06 (d, J=8.7 Hz, 1H, H^3), 4.8 (d, J=7.3 Hz, 1H, H^1), 5.1 (br, 1H, NH), [6.25 (d, J=3.3 Hz, 1H), 6.45 (dd, J=3.0 and 1.8 Hz, 1H), 7.45 (d, J=1.7 Hz, 1H furyl H, 7.5 and 7.8 (2×d, J=8.6 Hz, 2×2H, ArH), ν_{max} (film): 3300 (NH), 2900 (CH), 1788 (imide), 1706 (C=O imide),

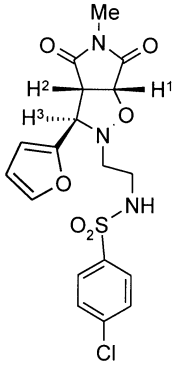
1586, 1436, 1331, 1289, 1163, 1094, 829, and 736 cm^{-1}. *m/z*(%) 235 (100) and 108 (87).

Enhancement (%)

Irradiated hydrogen	H¹	H²	H³
H¹		10.6	
H²	16.1		15.1
H³		18	



endo-Isomer (**30e**): Colourless needles from ethyl acetate–hexane, mp 164–166°C. (Found: C, 49.25, H, 4.25; N, 9.5, S, 7.2. $C_{18}H_{18}ClN_3O_6S$ requires: C, 49.15, H, 4.1; N, 9.55%); δ: 2.4 and 2.8 (2×m, 2H, CH_2NO), 3.08 (m, 5H, NMe and CH_2NH), 3.8 (d, J=8.0 Hz, 1H, H^2), 4.5 [broad peak at 20°C, (50°C. d, J=8.0 Hz, 1H, H^3], 4.9 (d, J=8.4 Hz, 1H, H^1), 5.0 (t, J=5.6 Hz, 1H, NH), [6.25 (d, J=3.3 Hz, 1H), 6.4 (dd, J=3.0 and 1.8 Hz, 1H), 7.4 (d, J=1.8 Hz, 1H, furyl H and 7.5–7.8 (2×d, 2×2H, J=8.6 Hz, ArH), *m/z*(%) 235 (93), 108 (100).



1.6. Single crystal X-ray diffraction analyses of 19 and 31

Crystallographic data for both structures were measured on a Nonius KappaCCD area-detector diffractometer using ω- and ψ-scans and MoKα radiation (λ=0.71073 Å). Both structures were solved by direct methods using SHELXS-86[20] and refined by full-matrix least-squares (based on F^2) using SHELXL-97.[21] The weighting scheme used is $w = [\sigma^2(F_o^2) + (0.0911P)^2 + 1.0092P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$. Refinement was the same for both structures in that all non-hydrogen atoms were refined with anisotropic displacement parameters whilst hydrogen atoms were constrained to predicted positions using a riding model. The residuals wR_2 and R_1, given below, are defined as $wR_2 = (\sum[w(F_o - F_c^2)^2]/\sum[wF_o^4])^{1/2}$ and $R_1 = \sum||F_o| - |F_c||/\sum|F_c|$.

1.6.1. Crystal data for 19. $C_{21}H_{22}ClN_3O_6S$, 0.71×0.59×0.22 mm, M=479.93, monoclinic, space group $P2_1/n$, a=10.3705(3), b=11.0506(2), c=19.4944(6) Å, β=100.613(2)°, V=2195.85(10) $Å^3$, Z=4, D_c=1.45 mg m^{-3}, μ=0.313 mm^{-1}, F(000)=1000, T=180 K.

Data collection. 2.13<2θ<26.00°; 4295 unique data collected of which 3808 with $F_o > 4.0\sigma(F_o)$ were considered 'observed'.

Structure refinement. Number of parameters=296, goodness of fit, s=1.071; wR_2 (all data)=0.0904, R_1 ('observed' data)=0.0335.

1.6.2. Crystal data for 31. $C_{13}H_{14}ClN_3O_3S$, 0.45×0.20×0.20 mm, M=327.78, monoclinic, space group $P2_1/n$, a=7.2618(1), b=21.6926(7), c=9.8547(3) Å, β=108.352(2)°, V=1473.43(7) $Å^3$, Z=4, D_c=1.48 mg m^{-3}, μ=0.41 mm^{-1}, F(000)=680, T=190 K.

Data collection. 2.18<2θ<26.0°; 2888 unique data collected of which 2552 with $F_o > 4.0\sigma(F_o)$ were considered 'observed'.

Structure refinement. Number of parameters=195, goodness of fit, s=1.024; wR_2 (all data)=0.0859, R_1 ('observed' data)=0.0319.

Supplementary data-sets for both structures, which include hydrogen co-ordinates, all thermal parameters and complete sets of bond lengths and angles, have been deposited at the Cambridge Crystallographic Data Centre and are available on request.

Acknowledgements

We thank Mersin University (Turkey) (H. A. D.) for leave of absence, Leeds University for support and Pfizer Pharmaceutical Company for a generous gift of compounds (**2**) and (**12**).

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