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1,3-Dipolar Cycloaddition Reactions of Levoglucosenone[1]

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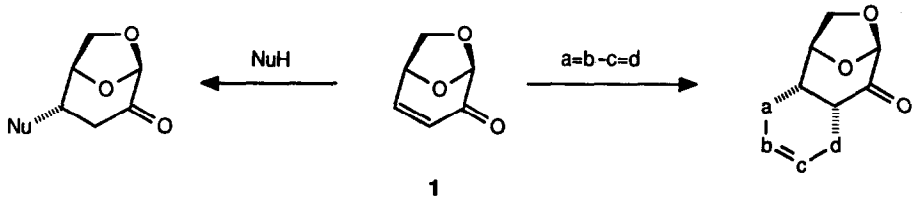
Abstract: The cycloaddition reactions of levoglucosenone with various 1,3-dipoles have been examined. Benzonitrile oxide underwent regiospecific and face-selective cycloaddition yielding isoxazoline **2a** as the major product. D-Glyceraldehyde-derived nitrile oxide **6** was less selective and afforded furazan *N*-oxide dimer **8** in addition to a mixture of isoxazolines. *C,N*-Diphenylnitrone and *N*-benzyl-*C*-phenylnitrone reacted similarly yielding isoxazolidines **9** and **10**. In each case the major adduct resulted from attack at the less hindered face of the dipolarophile *anti* to the 1,6-anhydro bridge, and with the oxygen of the nitrile oxide or nitrone becoming attached to the β-carbon of the enone. In contrast benzonitrile *N*-phenylimide added to levoglucosenone to give a regioisomeric mixture of pyrazoles **11** and **12**, resulting from dehydrogenation *in situ* of the initially formed pyrazolines. No reaction was observed with *p*-methoxybenzonitrile sulphide. The structures of isoxazoline **2a** and isoxazolidine **9** were confirmed by X-ray crystallography.

Levoglucosenone **1** is a cellulose-derived α,β–unsaturated bicyclic ketone which provides a useful source of both carbohydrate[2] and non-carbohydrate derivatives.[3] Its preparation[4] and various aspects of its chemistry have been studied in detail.[5-9] Of particular note is the high level of π-facial selectivity shown in some of its reactions. For example, Diels-Alder cycloadditions[7] and Michael additions[4,8] invariably take place at the less hindered *exo*-face *anti* to the 1,6-anhydro bridge (Scheme 1). Although both of these addition reactions have been exploited for stereoselective synthesis, the potential of levoglucosenone to act as the dipolarophile component in 1,3-dipolar cycloadditions has so far been neglected. We have investigated the reactions of levoglucosenone with several 1,3-dipoles and now report that these also take place regio- and stereo-selectively.



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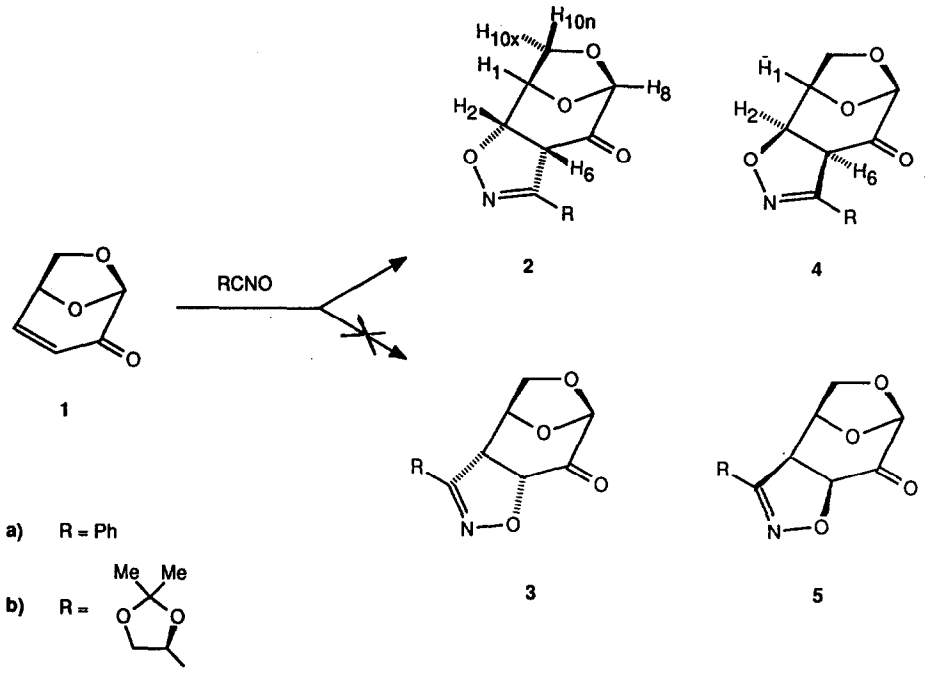
Scheme 1

Results and Discussion

Levoglucosenone was prepared from either acidified microcrystalline cellulose or waste newspaper using a modified version of literature methods.[5,10,11] Using an inverted pyrex tube held vertically in a flash vacuum pyrolysis (FVP) oven, 20-25 gram batches were heated at 350°C for 20 minutes at atmospheric pressure. The product was isolated in *ca* 5% overall yield from the pyrolysate which collected in the flask below the tube by chromatography and/or distillation. By this means 5 - 10 g quantities were prepared from 150 g of acidified cellulose.

Cycloaddition of Nitrile Oxides.- There are four possible 1:1 isoxazoline cycloadducts between levoglucosenone and a nitrile oxide: two regioisomers **2** and **3** resulting from approach of the 1,3-dipole to the *exo*-face of the alkene, and two corresponding isomers **4** and **5** due to *endo*-face attack. Benzonitrile oxide ($PhC{\equiv}N^{+}\text{-}O^{-}$) was selected to test the reactivity and selectivity of the α-enone unit in levoglucosenone. The competing dimerisation to 3,4-diphenylfurazan *N*-oxide[12] was minimised by generating the nitrile oxide *in situ* in the presence of an excess of the dipolarophile (1:4) by dehydrochlorination of benzohydroximoyl chloride (PhCCl=NOH).[12] A solution of the hydroximoyl chloride was added over 25 hours to a refluxing solution of levoglucosenone and triethylamine in benzene, and from the reaction mixture were isolated unreacted dipolarophile and two 1:1 adducts (Scheme 2).



Scheme 2

The major product was isolated as a white crystalline solid in 71% yield (based on benzonitrile oxide) and identified as isoxazoline **2a** on the basis of its spectroscopic properties. In the ^{1}H-NMR spectrum (Table 1) proton H(2) appears at higher chemical shift than H(6), thus establishing that the oxygen of the nitrile oxide is attached to the β–carbon of the α-enone unit of the dipolarophile. Supporting evidence is provided by ^{13}C-NMR absorptions at 155.1 (C-5), 80.9 (C-2) and 53.1 ppm (C-6), which are characteristic for carbons 3, 4 and 5 of the 2-isoxazoline ring.[13] Such a regiochemical preference is typical for reactions of nitrile oxides with α,β-unsaturated ketones, for example the addition of benzonitrile oxide to cyclohex-2-enone,[14] and is consistent with frontier orbital predictions.[15,16] The stereochemistry of the product was deduced from the magnitude of the ^{1}H-^{1}H coupling between H(1) and H(2). The low value (1.2 Hz) is similar to those reported[7] for Diels-Alder *exo*-face addition products and is consistent with the larger torsion angle H(1)-C(1)-C(2)-H(2) for **2a** compared with that for stereoisomer **4a**. There are also longer range couplings for H(1)-H(6) (^4J 0.6 Hz) and across the pyranose ring between H(2) and the anomeric proton H(8) (^5J 0.8 Hz). Other noteworthy features of the ^{1}H-NMR spectrum include the large 10.0 Hz coupling between H(2) and H(6), ie between the protons at the 4- and 5-positions of the *cis*-fused 2-isoxazoline moiety, and the strong solvent dependence of some of the chemical shifts (Table 1). Compared with $CDCl_3$ the signals in CD_3COCD_3 for protons H(2), H(6) and H(10) on the *endo*-face are shifted to higher frequency ($\Delta\delta_H$ 0.23, 0.49, 0.20 ppm respectively), whereas H(1), H(8) and H(10x) are affected little ($\Delta\delta_H$ 0.09, 0.02, 0.02 ppm). The remaining couplings involving H(10x), H(10n) and H(1) are typical for the

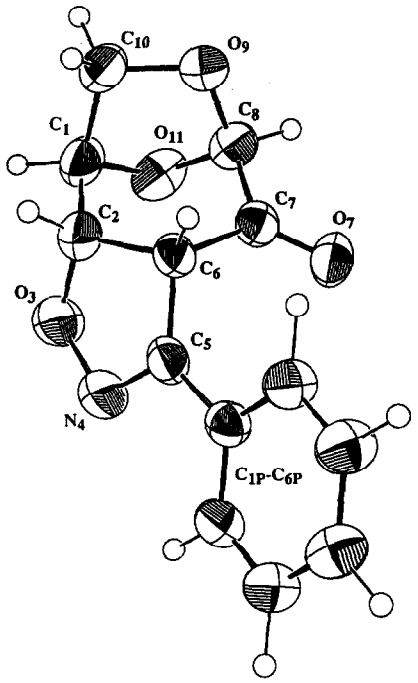
Table 1 Selected ^{1}H NMR data[a] for isoxazolines **2a, 4a, 2b** and isoxazolidines **9, 10**

		2a[b]	**4a**	**2b**[c]	**9**	**10**[d]		**2a**	**2b**[c]	**9**	**10**
$\delta_{H/C}$	H(1)	5.09(5.18)	4.71	5.00	5.05	4.85	C(1)	73.3	73.7	73.0[f]	73.0[f]
	H(2)	4.82(5.05)	5.49	4.71	4.64	4.39	C(2)	80.9	80.5	77.8	77.3
	H(5)	-	-	-	4.86	4.05	C(5)	155.1	154.7	70.7[f]	72.9[f]
	H(6)	4.49(4.98)	4.56	4.06	3.34	3.29	C(6)	53.1	53.9	58.5	57.0
	H(8)	5.19(5.17)	5.16	5.19	5.23	5.24	C(7)	191.6	191.9	196.4	197.5
	H(10x)	3.98(4.00)	3.82	3.91	3.96	3.89	C(8)	99.7	99.4	100.9	100.2
	H(10n)	4.01(4.21)	4.22	3.93	3.97	3.85	C(10)	65.2	65.2	65.8	65.6
J /Hz[e]	10x,10n	8.0	8.4	8.0	8.0	7.9					
	1,10x	4.8	4.8	4.1	4.0	4.7					
	1,10n	1.8	-	-	<1	1					
	1,2	1.2	6.2	0.9	1.3	-					
	2,6	10.0	11.2	10.2	6.8	7.5					
	5,6	-	-	-	4.5	6.7					

(a) Recorded in $CDCl_3$ unless otherwise stated; (b) also recorded in CD_3COCD_3 (δ_H); (c) for 1,3-dioxalan-5-yl substituent δ_H 4.96 (H-4'), 4.15 (H-5a'), 4.21 (H-5b'); $J_{4',5a'} = J_{4',5b'}$ 6.6 Hz, $J_{5a',5b'}$ 8.5 Hz; δ_C 110.6 (C-2'), 71.2 (C-5'), 66.8 (C-4'); (d) for benzyl substituent δ_H 3.97, 3.82; ^2J 14.3 Hz; δ_C 59.6 (CH_2); (e) long-range couplings: **2a** $^4J_{1,6}$ 0.6, $^5J_{2,8}$ 0.8 Hz; **2b** $^4J_{2,10x}$ 0.9 Hz; **9** $^4J_{1,6}$ 0.7 Hz; (f) alternative assignments.

conformationally-restrained levoglucosenone framework.[7,8] The regio- and stereo-chemical assignments were confirmed by X-ray crystallography. Figure 1 shows a stereochemical drawing of compound **2a**, together with a summary of its Cremer and Pople puckering parameters.[17] The atomic co-ordinates are given in Table 2.

The six-membered ring, which contains one sp^2-hybridised carbon, adopts a mainly $^1C_4$ conformation with some distortion due to the presence of the fused isoxazoline ring. The best plane through four atoms involves C(1), C(2), C(7) and C(8), and has C(6) 0.348 Å above and O(11) 0.788 Å below the plane; the puckering parameters are: Q = 0.609 Å, θ = 145.2° and ϕ = 189.2°. The 1,3-dioxolan rings in 1,6-anhydropyranoses[18] generally adopt a conformation between twist (3 atoms coplanar, $^{C(5)}T_{O(5)}$ where ϕ = 54°) and envelope forms (4 atoms coplanar, $E_{O(5)}$ where θ = 36°). In this case the puckering parameters (Q = 0.403 Å and ϕ = 51.0°) indicate that it has a near twist conformation with C(1) 0.262 Å above and O(11) 0.393 Å below the plane through C(8), O(9) and C(10). The isoxazoline ring is in the envelope form $E_{C(2)}$: the torsion angle for the O(3)-N(4)=C(5)-C(6) unit is 0.73° and C(2) lies 0.396 Å out of the best plane through these atoms. The phenyl ring substituent at C(5) is twisted by *ca* 20° out of the plane of the isoxazoline ring. The H-C-C-H torsion angles, calculated from the crystal structure data, are broadly in accord with the ^3J-values observed in the solution phase ^{1}H-NMR spectrum; the angles are compared with the observed and calculated couplings in Table 3.



Puckering parameters[a]

Ring	Q (Å)	θ (°)	ϕ(°)
pyranoid	0.609	145.2	189.2
dioxolan	0.403		51.0
isoxazoline	0.249		322.5

a) Ref 17; pyran ring: O(11) is atom 1, C(8) atom 2, etc; dioxalan ring: C(8) is atom 1, O(11) is atom 2, etc; *isoxazoline ring:* O(3) is atom 1, N(4) atom 2, etc

Figure 1. X-ray molecular structure, and Cremer and Pople puckering parameters for isoxazoline **2a**

Table 2. Fractional co-ordinates for isoxazoline **2a** and isoxazolidine **9**

	2a			**9**		
Atom	x	y	z	x	y	z
C(1)	-0.1328(7)	-0.8663(3)	-0.30135(14)	0.3266(4)	0.5029(3)	0.50066(22)
C(2)	-0.3051(7)	-0.7456(3)	-0.29562(13)	0.3183(4)	0.3678(3)	0.48700(22)
O(3)	-0.1728(5)	-0.62201(22)	-0.27875(10)	0.2102(3)	0.34946(24)	0.42198(15)
N(4)	-0.2953(7)	-0.5062(3)	-0.30602(12)	0.2388(3)	0.22747(24)	0.38899(19)
C(5)	-0.4423(7)	-0.5501(3)	-0.34900(12)	0.3969(4)	0.2285(3)	0.37116(20)
C(6)	-0.4367(6)	-0.7046(3)	-0.35735(12)	0.4560(4)	0.3098(3)	0.44719(24)
C(7)	-0.3006(6)	-0.7505(3)	-0.41741(13)	0.5651(4)	0.4001(4)	0.4132(3)
O(7)	-0.3124(5)	-0.69089(21)	-0.46779(8)	0.6687(4)	0.3697(3)	0.37090(25)
C(8)	-0.1434(6)	-0.8780(3)	-0.40774(14)	0.5383(5)	0.5310(4)	0.4338(4)
O(9)	-0.2893(5)	-0.98935(19)	-0.38715(9)	0.5673(3)	0.5496(4)	0.5263(3)
C(10)	-0.2658(8)	-0.9981(3)	-0.31833(13)	0.4316(4)	0.5353(5)	0.5736(3)
O(11)	+0.0176(4)	-0.84769(22)	-0.35721(11)	0.3928(3)	0.55790(24)	0.42282(20)
C(1P)	-0.6013(4)	-0.45241(18)	-0.38358(8)	0.45995(25)	0.10377(15)	0.36944(16)
C(2P)	-0.5744	-0.31011	-0.37466	0.40639	0.01129	0.42282
C(3P)	-0.7380	-0.21844	-0.40298	0.46333	-0.10504	0.41624
C(4P)	-0.9285	-0.26906	-0.44022	0.57380	-0.12887	0.35628
C(5P)	-0.9554	-0.41135	-0.44914	0.62735	-0.03639	0.30291
C(6P)	-0.7918	-0.50303	-0.42082	0.57043	0.07993	0.30948
C(7P)				0.14526(23)	0.20912(21)	0.31438(12)
C(8P)				0.01660	0.27347	0.30820
C(9P)				-0.07899	0.24974	0.23924
C(10P)				-0.04592	0.16165	0.17645
C(11P)				0.08274	0.09729	0.18261
C(12P)				0.17833	0.12103	0.25159

The minor 1:1 adduct, which was isolated in 0.6% yield, was assigned structure **4a** also on the basis of its ^{1}H-NMR spectrum. That it has the same stereochemistry as isoxazoline **2a** is evident from the higher chemical shift (5.49 ppm) for H(2) compared with that for H(6) (4.56 ppm). It must therefore have opposite stereochemistry at C(2) and C(6), and have been formed by *endo*-face attack by the 1,3-dipole. Further supporting evidence for the proposed structure is provided by the larger ^3J value for H(1)-H(2) (6.2 cf 1.2 Hz for **2a**), the absence of the H(1)-H(6) coupling, and a new W-coupling between H(2) and H(10x) not observed for isomer **2a**. The formation of isoxazoline **4a**, albeit in very small amounts, represents a rare case of reaction at *endo*-face of levoglucosenone. Despite a careful examination of the reaction mixture neither of the alternative regioisomers **3a** and **5a** could be detected. The cycloaddition is therefore regiospecific and highly selective (100:1) in favour of attack from the less hindered *exo*-face of the dipolarophile.

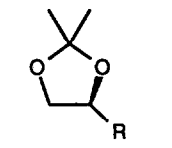
In contrast the D-glyceraldehyde nitrile oxide **6** proved to be less selective. It was generated by dehydrochlorination of hydroximoyl chloride **7**, which is readily accessible from D-mannitol by established literature procedures.[20] Reaction with levoglucosenone (1:2) afforded furazan *N*-oxide **8** (28%), the dimer of nitrile oxide **6**, and a mixture of isoxazoline cycloadducts in a combined yield of 58% and in the ratio 16:12:1 by NMR. Only the major product could be purified fully. Trituration and crystallisation afforded a white solid which was identified as isomer **2b**, ie having the same regio- and stereo-chemistry as the main

Table 3 Selected H-C-C-H torsion angles (°) for isoxazoline **2a** and isoxazolidine **9**, with observed and calculated[a] coupling constants (Hz)

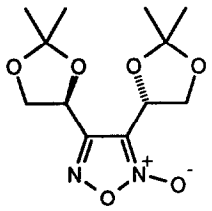
Compound		H_x,H_y 1,2	1,10n	1,10x	2,6	5,6
2a	angle	-68.2	84.0	-38.1	-23.1	-
	J(obs)	1.2	1.8	4.8	10.0	-
	J(calc)	2.1	1.4	5.3	6.9	-
9	angle	-72.1	91.0	-31.3	-13.9	-129.4
	J(obs)	1.3	<1	4.0	6.8	4.5
	J(calc)	1.8	1.4	6.1	7.6	5.1

a) $^3J = 7.76\cos^2\theta - 1.1\cos\theta + 1.4$ (ref. 19)

product from the corresponding reaction with benzonitrile oxide. The NMR data for both the carbohydrate and isoxazoline portions of the two molecules are very similar to those of **2a** (Table 1). In view of the established preference for *exo*-face addition the second product was tentatively assigned structure **3b**, the *exo*-face regioisomer of **2b**, and the third minor product was assumed to have structure **4b** resulting from *endo*-attack. It is concluded that nitrile oxide **6** is less reactive and less regioselective towards levoglucosenone than benzonitrile oxide. The lower yields of adducts and the formation of significant quantities of furazan *N*-oxide **8** can be attributed to the greater tendency of the nitrile oxide to dimerise.



6 R = CNO
7 R = CCl=NOH



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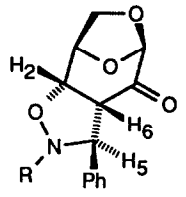
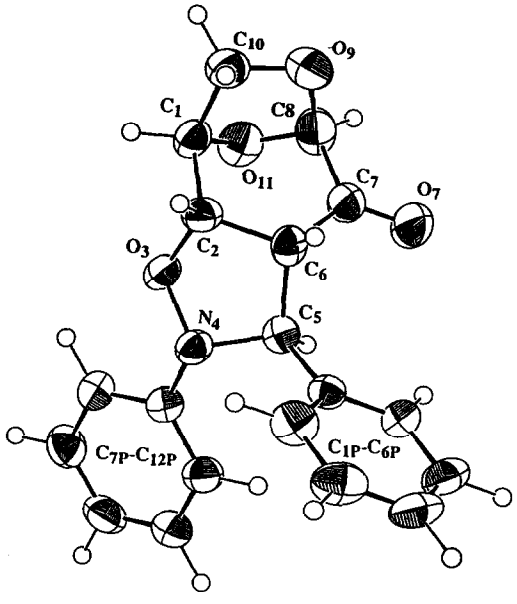


9 R = Ph
10 R = Bn

Cycloaddition of Nitrones.- Addition of a nitrone to levoglucosenone could give rise to eight possible 1:1 adducts: *exo*- and *endo*-isoxazolidine isomers for each pair of regioisomers resulting from attack at the *exo*- and *endo*-faces of the dipolarophile. Treatment of levoglucosenone with a slight excess (1:1.04) of *C,N*-diphenylnitrone ($PhCH=N^+Ph\text{-}O^-$) in refluxing toluene for two days gave a single 1:1 adduct in 68% yield. It was assigned structure **9** on the basis of its ^{1}H-NMR data (Table 1). The greater chemical shift for H(2) (4.64 ppm) compared with H(6) (3.34 ppm) shows that the oxygen of the nitrone is attached to the β-carbon of the enone, and the small H(1)-H(2) coupling (1.3 Hz) similar to that described above for

isoxazolines **2a** and **2b** indicates *exo*-face approach of the nitrone to the dipolarophile. The stereochemistry at C(5), originally the prochiral carbon of the nitrone, could not be deduced from the coupling (4.5 Hz) and was determined by NOE measurements. Irradition of H(5) had no effect on H(2) and caused only a small enhancement (1.5%) of vicinal proton H(6). Conversely irradition of H(2) strongly enhanced, as expected, both H(1) (5.3%) and H(6) (8.5%), but did not increase the H(5) signal. These observations strongly favour structure **9** which arises from *endo*-approach of the nitrone to the *exo*-face of the alkene, thus forming the isoxazolidine ring with H(5) anti to the ring junction protons H(2) and H(6). None of the other seven possible 1:1 adducts were detected.

The structure of isoxazolidine **9** was confirmed by X-ray crystallography. There is significant distortion of the pyranoid ring from the $^1C_4$ conformation [C(6) lies 0.132 Å above and O(11) 0.806 Å below the best plane through C(1), C(2), C(7) and C(8)] towards $sofa_O$ where five atoms are coplanar; O(11) lies 0.789 Å below the best plane through the five carbon atoms. The conformation of the 1,3-dioxolan ring also differs markedly from that observed for compound **2a**. The puckering parameters (Q = 0.396 Å and ϕ = 39.8°) show that it is mainly in the $E_{O(11)}$ form, with O(11) 0.595 Å out of the plane through C(1), C(8), O(9) and C(10). Whereas the isoxazoline ring in compound **2a** adopts an envelope arrangement, the isoxazolidine in analogue **9** is predominantly twist $^{O(3)}T_{N(4)}$ with O(3) 0.389 Å above and N(4) 0.303 Å below the plane through C(2), C(5) and C(6). The H-C-C-H torsion angles, calculated from the X-ray data, are compared with the observed and calculated ^{1}H-NMR couplings in Table 3. A stereochemical drawing and puckering parameters for the three ring systems are shown in Figure 2.



Puckering parameters[a]

Ring	Q (Å)	θ (°)	φ(°)
pyranoid	0.604	132.2	176.7
dioxolan	0.396		39.8
isoxazoline	0.431		15.9

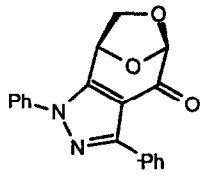
a) Ref 17; pyran ring: O(11) is atom 1, C(8) atom 2, etc; dioxalan ring: C(8) is atom 1, O(11) is atom 2, etc; isoxazoline ring: O(3) is atom 1, N(4) atom 2, etc

Figure 2. X-ray molecular structure, and Cremer and Pople puckering parameters for isoxazolidine **9**

The addition of *N*-benzyl-*C*-phenylnitrone proceeded similarly. The reaction was highly selective affording only a single adduct in 87% yield. This was assigned structure **10** by comparison of its ^{1}H- and ^{13}C-NMR data with those of *N*-phenylisoxazolidine **9** (Table 1). Again NOE measurements established the *anti*-arrangement of H(5) and H(6).

Reactions with Other 1,3-Dipoles.- Having established that nitrile oxides cycloadd readily to levoglucosenone other examples of nitrilium betaines were examined.

Benzonitrile *N*-phenylimide (diphenylnitrilimine, PhC≡N^{+}-N^{-}Ph) was generated by dehydrochlorination of the corresponding hydrazonoyl chloride (PhCCl=NNHPh) in the presence of levoglucosenone (1:1.5) using triethylamine in toluene under reflux. From the reaction mixture was isolated an 8:1 regioisomeric pair of pyrazoles **11** and **12** in a combined yield of 62%. There was no evidence for the presence of the initially formed 2-pyrazoline cycloadducts, and it is presumed that these are oxidised under the reaction conditions. A very similar facile oxidation of 2-pyrazoline cycloadducts has been reported[15] for the corresponding reaction of benzonitrile *N*-phenylimide with 2-cyclohexenone yielding pyrazoles **13** and **14**.



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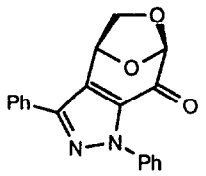

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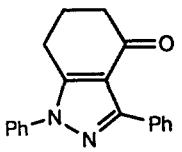

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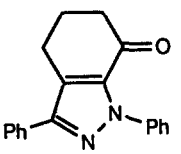

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The individual isomers **11** and **12** were separated by chromatography and characterised by their analytical and spectroscopic properties. In the mass spectrum both compounds show parent ion peaks at *m/z* 318 with similar fragmentation patterns, and both have the expected ^{1}H-NMR signals for the phenyl and levoglucosenone moieties. Moreover, the absence of ring junction protons at C(2) and C(6) meant that the individual isomers could not be assigned unambiguously solely on the basis of their ^{1}H- and ^{13}C-NMR chemical shifts. Instead identification was made with the aid of NOE experiments (Fig. 3). For the major isomer the *ortho*-protons of one of the phenyl substituents are deshielded (δ_H 8.29). These were assigned to the C-phenyl group at C(5) in structure **11** by analogy with the chemical shifts reported[21] for diphenylpyrazole **13**, the structure of which has been established unambiguously and which has one pair of *ortho*-protons resonating at high frequency (8.0-8.2 ppm). Irradition of the *ortho*-protons at 8.29 ppm in compound **11** enhanced the PhC *meta/para*-proton signals strongly (10%), but had no effect on H(1); irradiation of H(1) enhanced H(10x) (3%) and the PhN *ortho*-protons (1.5%) but had no effect on PhC *ortho*-proton signals. These results support the assignment of structure **11** to the major adduct. The regioselectivity (8:1) is less than the corresponding reaction with benzonitrile oxide but still favours the same orientation.

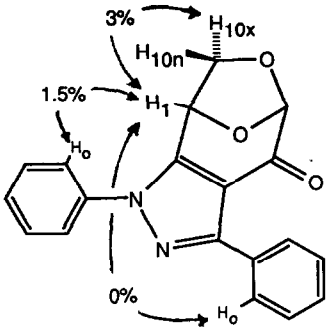
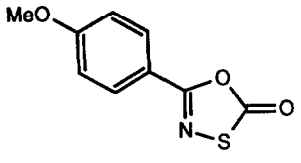


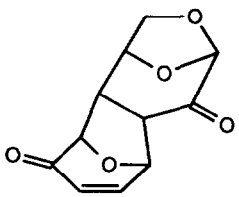
Figure 3 Selected NOE data for pyrazole **11**



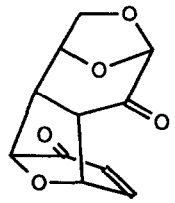
15

Finally an attempt was made to react levoglucosenone with *p*-methoxybenzonitrile sulphide. Nitrile sulphides ($RC{\equiv}N^{+}\text{-}S^{-}$) are short-lived intermediates[22] prone to fragment to sulphur and nitriles, but have been trapped by reactive dipolarophiles such as dimethyl acetylenedicarboxylate and acrylate esters. The nitrile sulphide was generated by thermal decarboxylation of *p*-methoxyphenyloxathiazolone **15**[23] in the presence of levoglucosenone (1:2) in refluxing xylene. However, the only products isolated were sulphur (89%) and *p*-methoxybenzonitrile (81%), and the expected 2-isothiazoline cycloadducts could not be detected.

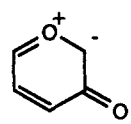
Prior to the present work the only example of 1,3-dipolar cycloaddition to levoglucosenone involved formation of the thermolysis products **16** and **17**, which were believed[5] to result from initial cycloreversion to formaldehyde and 3-oxidopyrylium **18**, followed by cycloaddition of this carbonyl ylide to further levoglucosenone. In conclusion the results described in this paper provide a further illustration of the high degree of π-facial selectivity in the reactions of levoglucosenone exerted by the 1,6-anhydro bridge. The ready access to the isoxazoline and isoxazolidine derivatives also offers scope for further stereoselective synthesis.[12]



16



17



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Experimental

The instrumentation used for recording IR, ^{1}H- and ^{13}C-NMR and mass spectra, and the chromatographic methods were as previously described.[13] Benzohydroximoyl chloride,[24] 4R-4-chloro-ximino-2,2-dimethyl-1,3-dioxalan,[20] *N*-benzyl-*C*-phenylnitrone,[25] *N*-phenylbenzohydrazonoyl chloride,[27] and 5-(*p*-methoxyphenyl)-1,3,4-oxathiazol-2-one[23] were prepared by established literature procedures.

Preparation of Levoglucosenone **1**.- This was prepared by adapting the general method of Shafizadeh[4] with the modification of Furneaux.[5] To a suspension of cellulose powder or shredded newspaper (150 g) in ethanol (400 ml) was added 88% orthophosphoric acid (3.4 g). After removal of the solvent under reduced pressure the residual cellulose powder (with 2% w/w acid catalyst) was pyrolysed in batches of *ca* 20 g in an inverted pyrex tube using a vertical furnace (350°C, 20 min, 1 atm). The oily material which collected in the flask below the tube were dissolved in chloroform (200 ml), washed with saturated aq. $NaHCO_3$ (2 x 200 ml), water (200 ml), dried ($MgSO_4$), and concentrated to afford a pale green oil. Pure levoglucosenone was obtained (7.75 g, 5%) by chromatography (silica, hexane-EtOAc 85/15) and/or distillation, b.p. 60-63°C at 0.2 mmHg (lit.,[4] 68-72°C at 0.7 mmHg), $[\alpha]_D^{32}$ -550° (c=1.0, $CHCl_3$)(lit.,[4] -530°).

Cycloaddition of Benzonitrile Oxide.- To a stirred solution of levoglucosenone **1** (171 mg, 1.36 mmol) and triethylamine (50 mg, 0.5 mmol) at reflux in dry benzene (10 ml) was added a solution of benzohydroximoyl chloride (56 mg, 0.36 mmol) in benzene (5 ml) during 25 h using a motorised syringe. The mixture was heated for a further 16 h, filtered through celite, concentrated and the residue separated by preparative TLC (silica, hexane-EtOAc 3:1) to afford unreacted **1** (106 mg, 62%) and two 1:1 adducts:-

1R,2S,6R,8R-5-Phenyl-3,9,11-trioxa-4-azatricyclo[6.2.1.0^{2,6}]undec-4-en-7-one **2a** (62 mg, 71%) as clear prisms, m.p. 177-178°C (from Et_2O) (Found: C, 63.7; H, 4.6; N, 5.7. $C_{13}H_{11}NO_4$ requires C, 63.7; H, 4.5; N, 5.7%); $[\alpha]_D^{32}$ +146° (c=0.50, $CHCl_3$); ν_{max}(Nujol) 1750 (C=O), 1560 cm^{-1}(C=N); m/z 245(M^+), 217[(M-CO)$^+$], 188, 171, 144 and *1R,2R,6S,8R-5-Phenyl-3,9,11-trioxa-4-azatricyclo[6.2.1.0^{2,6}]undec-4-en-7-one* **4a** (1 mg, 0.6%), m.p. 134-135°C (from hexane-Et_2O) (*m/z* 245.0675 $C_{13}H_{11}NO_4$ requires M^+ 245.0688); NMR data - see Table 1.

Cycloaddition of Nitrile Oxide **6**.- To a stirred solution of levoglucosenone (1.04 g, 8.25 mmol) and triethylamine (0.44 g, 4.4 mmol) in dry diethyl ether (60 ml) at 0°C was added a solution of hydroximoyl chloride **7** (0.72 g, 4.0 mmol) in diethyl ether (40 ml) during 3 h, and the mixture stirred for a further 16 h at room temperature. After removal of precipitated $Et_3N.HCl$ by filtration, the solution was concentrated and chromatographed (silica, hexane-EtOAc 4:1) to yield in order of elution unreacted **1** (441 mg, 42%), furazan *N*-oxide **8** (125 mg, 22%) and a mixture of three 1:1 cycloadducts (624 mg, 58%) in the ratio 16:12:1 by NMR analysis. The major isomer was isolated from the mixture by trituration (hexane - CH_2Cl_2) and identified as *1R,2S,6R,8R-5-(4R-2,2-dimethyl-1,3-dioxalan-4-yl)-3,9,11-trioxa-4-azatricyclo[6.2.1.0^{2,6}]undec-4-en-7-one* **2b**, m.p. 152°C (Found: C, 53.4; H, 5.7; N, 5.2. $C_{12}H_{14}NO_6$ requires C, 53.5; H, 5.6; N, 5.2%); $[\alpha]_D^{24}$ -121° (c=0.5, Me_2CO); ν_{max} (Nujol) 1740 cm^{-1} (C=O); NMR data - see Table 1.

Cycloaddition of C,N-*Diphenylnitrone*.- A solution of levoglucosenone (0.71 g, 5.6 mmol) and *C,N*-diphenylnitrone (1.14 g, 5.8 mmol) in dry toluene (20 ml) was heated under reflux for 2 days. After concentration the mixture was separated by chromatography (silica, hexane - EtOAc 7:3) to afford a single 1:1 adduct *1R,2S,5S,6R,8R-4,5-diphenyl-3,9,11-trioxa-4-azatricyclo[6.2.1.0^{2,6}]undecan-7-one* **9** (1.23 g, 68%) as clear prisms, m.p. 176-177°C (from Et_2O) (Found: C, 70.4; H, 5.3; N, 4.3. $C_{19}H_{17}NO_4$ requires C, 70.6; H, 5.3; N, 4.3%); $[\alpha]_D^{33}$ -100° (c=0.5, $CHCl_3$); ν_{max} (Nujol) 1730 cm^{-1} (C=O); *m/z* 323(M^+); NMR

data - see Table 1.

Cycloaddition of N-*Benzyl*-C-*phenylnitrone*.- The procedure used was as for the diphenylnitrone above. From the reaction mixture was isolated a single 1:1 adduct *1R,1S,5S,6R,8R-4-benzyl-5-phenyl-3,9,11-trioxa-4-azatricyclo [6.2.1.0^{2,6}]undecan-7-one* **10** (87%) as needles, m.p. 138-139°C (from EtOH) (Found: C, 71.1; H, 5.6; N, 4.3. $C_{20}H_{19}NO_4$ requires C, 71.2; H, 5.7; N, 4.1%); $[\alpha]_D^{24}$ -213° (c=1.0, $CHCl_3$); ν_{max} (Nujol) 1720 cm^{-1} (C=O); *m/z* 337(M^+); NMR data - see Table 1

Cycloaddition of Benzonitrile N-*Phenylimide*.- A solution of triethylamine (0.30 g, 3.0 mmol) in dry toluene (5 ml) was added dropwise to a solution of *N*-phenylbenzohydrazonoyl chloride (172 mg, 0.75 mmol) and levoglucosenone (141 mg, 1.1 mmol) in toluene (10 ml) under nitrogen at room temperature. The mixture was heated under reflux for 1.5 h, filtered through celite and concentrated. Flash chromatography (silica, hexane - EtOAc 4:1) afforded *1S,8R-3,5-diphenyl-2,6-dehydro-9,11-dioxa-3,4-diazatricyclo[6.2.1.0^{2,6}]undec-4-en-7-one* **11** (131 mg, 55%), pale yellow prisms, m.p. 185°C (from EtOH); $[\alpha]_D^{29}$ -118° (c=0.5, $CHCl_3$); ν_{max}(Nujol) 1690 cm^{-1} (C=O); *m/z* 318(M^+), 290[(M-CO)$^+$], and *1S,8R-3,5-diphenyl-2,6-dehydro-9,11-dioxa-4,5-diazatricyclo[6.2.1.0^{2,6}]undec-3-en-7-one* **12** (17 mg, 7%), m.p. 179°C (from EtOH) (Found: C, 71.7; H, 4.4; N, 8.7. $C_{19}H_{14}N_2O_3$ requires C, 71.7; H, 4.4; N, 8.8%); $[\alpha]_D^{28}$ -167° (c=0.5, $CHCl_3$); ν_{max}(Nujol) 1705 cm^{-1} (C=O); *m/z* 318(M^+), 290 [(M-CO)$^+$].

Attempted Cycloaddition of p-*methoxybenzonitrile Sulphide*.- A solution of 5-(*p*-methoxyphenyl)-1,3,4-oxathiazol-2-one **15** (257 mg, 1.23 mmol) and levoglucosenone (310 mg, 2.5 mmol) in dry xylene (25 ml) was heated under reflux for 16 h. Separation of the mixture by preparative TLC afforded sulphur (35 mg, 89%) and *p*-methoxybenzonitrile (132 mg, 81%).

Crystal structures of isoxazoline **2a** *and isoxazolidine* **9**.- Data for **9**, where different from **2a**, are given in square brackets. Fractional co-ordinates for atoms with standard deviations are given in Table 2; bond lengths and angles, torsion angles, observed and calculated structure factors, and anisotropic vibration parameters are deposited with the Cambridge Crystallographic Data Centre (CCDC), UK.

(a) *Crystal data*. $C_{13}H_{11}NO_4$, M = 245.2 [$C_{19}H_{17}NO_4$, M = 323.3], orthorhombic, space group $P2_12_12_1$; a = 5.5044(2) [9.2952(4)], b = 9.6596(6) [11.0635(4)], c = 20.9223(9) [15.1210(6)] Å; V = 1112.2 [1550.0]Å^3, Z = 4, D_{calc} = 1.464 [1.381] g cm^{-3}, T = 295 K, colourless prisms, 0.35 x 0.23 x 0.12 [0.62 x 0.66 x 1.08] mm, μ(Cu K_α) = 8.80 [7.80] cm^{-1}, F(000) = 512 [680].

(b) *Data collection and processing*. STADI-4 four-circle diffractometer, graphite-monochromated Cu K_α X-radiation , T = 300 K, $\omega/2\theta$, ω = 0.68 + 0.35 tanθ°, 1183 [1285] unique data ($2\theta_{max}$ = 60°, h:0->6 [10], k: 0->10 [12], l = 0->23 [16]) collected of which 997 [1256] with $F>6\sigma(F)$ for use in all calculations. An empirical absorption correction was made using ψ-scans.[27] No significant crystal decay or movement was apparent.

(c) *Structure solution and refinement*. Automatic direct methods[28] located all non-hydrogen atoms which were then refined anisotropically; iterative cycles of least-squares refinement and difference Fourier synthesis indicated hydrogen atoms which were thereafter refined in fixed, calculated positions with a common isotropic thermal parameter (U = 0.081(3) [0.094(5)] Å^2. The phenyl rings were constrained to be ideal, rigid hexagons. A secondary extinction parameter refined to 0.022(2)[0.239(10)]. The weighting scheme $w^{-1} = \sigma^2(F) + 0.000179$ [0.008388]F^2 gave satisfactory agreement analyses, and in the final cycle, the maximum Δ/σ was 0.004[0.217]. At the final convergence R and R_w were 0.0333 and 0.0436[0.0571, 0.0950], respectively, for 153[195] parameters. The final difference Fourier synthesis revealed no feature

above 0.17[0.27] *e* Å^{-3}. Inlaid atomic scattering factors were used, molecular geometry calculations utilised CALC,[29] and the Figures were produced by ORTEP.[30]

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