Tetrahedron Vol. 49, No. 36, pp. 8179-8194, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

STERIC ACCELERATION OF INTRAMOLECULAR CYCLOADDITION REACTIONS

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(*Received in USA* 10 *March* 1993; *accepted* 19 *May* 1993)

Abstract: Use of conformational constraints, induced by different *ortho*-substituents in 1-allyloxy-2-(substituted)methylbenzenes, where the substituent is a 1,3-dipole such as the azide or 3-oxidopyridinium group, can be employed to accelerate the 1,3-dipolar cycloaddition reaction. In this manner cycloadditions that otherwise do not proceed can be forced to react.

A variety of methods have been used to facilitate cycloaddition reactions, including studies on the effect of pressure,[1] catalysts,[2] solvent,[3] substituent[4] and strain effects.[5] Intramolecularity can also give an entropy advantage to cycloadditions by increasing the rate of approach between the reactants and any structural feature which enhances the encounter rate should assist the rate of reaction.[6] Herein we describe a simple chemical system of use in increasing reaction rates and in which the steric effect of different groups can be directly compared. The system involves steric restriction of the conformationally allowed space which the reactants can occupy, hence favouring their chances of approach. The system is illustrated in Figure 1.

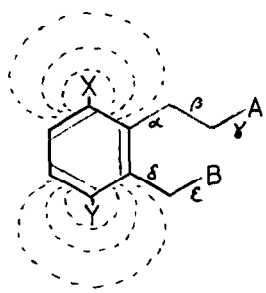
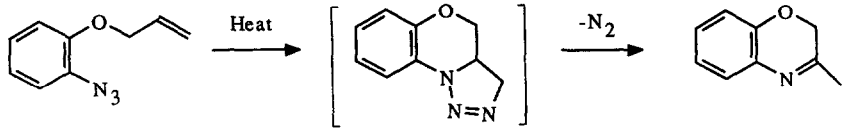


Figure 1. A and B are interacting groups, *e.g.* dipolarophile and dipole respectively. Rotation is allowed around the links by changing the conformational angles around the bonds α, ß, ɣ, δ and ε. X and Y are steric buttresses used to restrict the conformational space that can be occupied by groups A and B.

The two reactants (A, B, *e.g.* a dipole and a dipolarophile) are linked by short handles to a benzene ring and the steric effect of different *ortho*-substituents on the rate of reaction examined. For example, with increasing size of the steric buttresses, X and Y, rotations about the handles (about bonds α, ß, τ, δ and ε) are all affected, with the consequence that the conformationally allowed volume that the substituents A and B can occupy is progressively decreased. Although molecular modelling packages exist that can be used to estimate these conformational changes,[7] it is more difficult to make allowances for the steric approach required in the transition state leading to the reaction. These effects can be studied with our model system and herein we report results on two different 1,3-dipolar cycloaddition reactions.

A. Azides

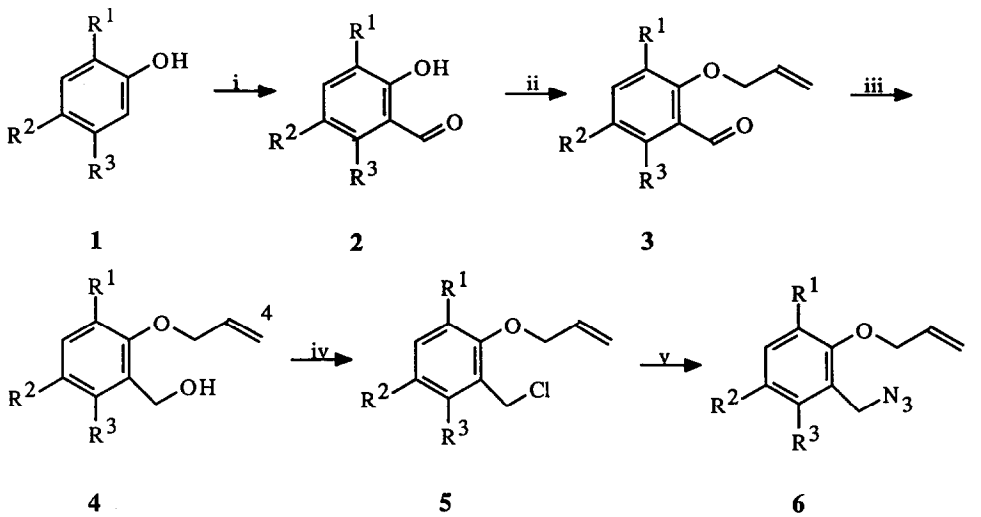
The simplest system we have studied is based on the 2-allyloxybenzylazides **6**, which, on cycloaddition, lead to the novel seven-membered, oxazepine cycloadducts **7**. The related phenylazides **8** have been studied by Fusco *et al.*,[8] which were reported to cycloadd with concomitant loss of nitrogen to form cycloadducts of the type **10**, the presumed triazoline intermediates, **9**, being too thermally unstable to



8 **9** **10**

isolate. Our system has the advantage that neither the dipole nor dipolarophile are directly conjugated to the aromatic ring and any through-bond electronic effects of aromatic ring substituents, being homoconjugate, were expected to be only of minor significance.

Entry to the systems **6** were as outlined in Scheme 1. Selective *ortho*-formylation of the parent phenol, **1**, was carried out using the method of Casiraghi, *et al.*[9] Allylation, or propargylation, of the phenolic group, followed by sodium borohydride reduction of the aldehyde function afforded the benzylic alcohols, **4**, which proved a convenient point for purification and storage. Generally, samples of the alcohols were chlorinated, to give the moisture sensitive benzylic chlorides **5** and then immediately reacted with sodium azide to give the target azides, **6**. The azides were freshly prepared before studying their cycloaddition behaviour. Cycloaddition reactions were generally carried out in solutions of benzene, or for monitoring by ^{1}H n.m.r. spectroscopy, in deuteriochloroform in n.m.r. tubes sealed under reduced pressure.



1 **2** **3**

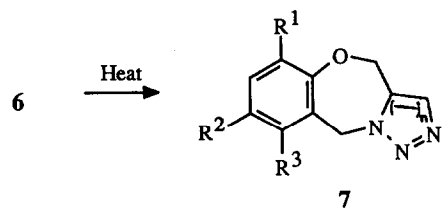
4 **5** **6**

Scheme 1:
i, $SnCl_4$, NEt_3, $(CH_2O)_3$; ii, allyl bromide, K_2CO_3, MeCN; iii, $NaBH_4$, MeOH;
iv, $(COCl)_2$, DMF, CH_2Cl_2; v, NaN_3, DMSO.

The parent azide **6a** only cycloadded slowly at 80°, disappearance of the vinylic signals taking over 7 days, producing one major product, identified as the expected cycloadduct **7a**, in moderate yield. Attempts to speed up the reaction by increasing the temperature lead to lower cycloadduct yields,

presumably because of degradation of the starting azide. The product triazoline, **7a**, proved to be thermally stable at 80° but unstable to either acid or silica gel chromatography, *vide infra*. Its ^{1}H n.m.r. spectrum showed the ring methylene groups as AB quartets and a detailed inspection of the coupling constants (Figure 2) indicated that it adopts a folded conformation in which the triazoline ring sits over the benzene ring.[10]

The slow rate of cycloaddition of the parent system encouraged us to investigate the *ortho*-substituent effect. Substitution of a single methyl group adjacent to the allyloxygroup, **6b**, was examined since the allyloxy has more rotational degrees of freedom than the benzyl azide function; steric hindrance between the methyl group and the methylene and vinyl groups of the allyloxy substituent severely restricts the space the latter can adopt, including the preferred conformations expected for the parent, unsubstituted compound **6a**. On heating, a 20-fold increase in reaction rate was observed, disappearance of starting material occurring within 10 h, accompanied by clean formation of the triazoline **7b** (measured E_{act} 123 10 kJ mol^{-1}). No sign of decomposition of the triazoline to produce imines or aziridines could be detected at temperatures up to 120°.



7

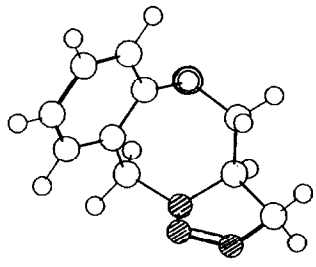


Figure 2: Conformational view of the cycloadduct **7a**

a $R^1 = R^2 = R^3 = H$, n=0
b R^1 = Me; $R^2 = R^3 = H$, n=0
c $R^1 = R^2 = {}^t$Bu; $R^3 = H$, n=0
d $R^1 = R^2$ = Br; R^3 = H, n=0
e $R^1 = R^3$ = Me; $R^2 = H$, n=0
f $R^1 = R^2 = R^3 = H$, n=1
g $R^1 = R^2 = {}^t$Bu; $R^3 = H$, n=1
h $R^1 = R^2$ = Br; $R^3 = H$, n=1

The next substituent studied was the t-butyl group. For synthetic convenience the di-t-butyl derivative **6c** was prepared; it was assumed that the 4-t-butyl group would not have a significant effect on the rate of cycloaddition. Examination of models showed that a t-butyl group should cause a further, dramatic reduction in the space available to the allyloxy group and hence show an accelerated cycloaddition rate. An estimate of this conformational restriction was obtained by rotating about the mobile bonds (Figure 1) in 30° increments and dismissing those conformations in which the allyloxy and azidomethylene group encroached the conformational space of the other or the *ortho*-substituent, *i.e.*, those conformations where adverse van der Waals' interferences occurred. Of the total possible conformations (12^5 = 248832), allowed values for **6a**:**6b**:**6c** of 159176(63%):119528(48%):59878(24%) were calculated, indicating that the t-butyl series **6c** should show a further dramatic rate increase in the rate of cycloaddition.[11]

On heating **6c** at 80° the reaction again proceeded smoothly to give the expected, stable triazoline **7c**, disappearance of starting material being observed within 7 h (measured E_{act} 74±10 kJ mol $^{-1}$). Although this was clearly faster than for the methyl derivative **6b**, the difference was less than had been anticipated. A possible explanation for this minor acceleration could be the onset of an unfavourable interaction between the bulky t-butyl group and the methylene protons on the allyloxy group in the conformation required to allow favourable alignment of the dipole and dipolarophile as they approach the cycloaddition (Figure 3).

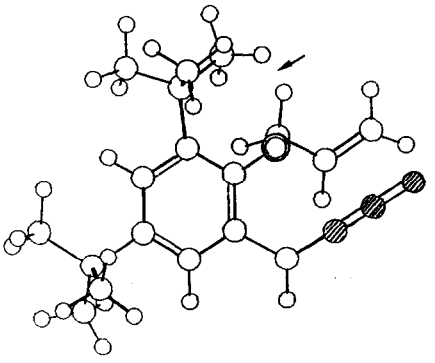


Figure 3: Predicted steric clash in cycloaddition of the azide **6c**

Thus, as in examples demonstrated for interactions within the active site of enzymes,[12] for our simple model system, too high a restriction of the available conformational space for the allyloxy group by large *ortho*-substituents may also exclude those conformations required for cycloaddition!

As a further example of steric buttressing in this series, the effect of a bromo-substituent has been examined, since this is considered to be of similar steric size to that of a methyl group.[13] For synthetic convenience the dibromide series **6d** was prepared. Cycloaddition was indeed faster than for the parent, unsubstituted series, **7d** being produced with a measured E_{act} of 132±10 kJ mol $^{-1}$, very similar to the value observed for the mono-methyl analogue **6a**. Of course, conformational restrictions could not only be produced by unfavourable van der Waals' interaction between substituents but also by electrostatic field repulsions (or attractions). A study of the effect of a fluoro-group in place of hydrogen and of a trifluoromethyl group in place of the methyl group would be of interest.

The above examples involve only one *ortho*-substituent. It was pertinent to select one example in which the steric effect of *ortho*-substituents to both the allyloxy and the azidomethyl group were present. The dimethyl analogue **6e** was therefore prepared. Models indicated that the effect of the second methyl group would be marginal, since the azidomethyl group has fewer degrees of freedom than the allyloxy group and the linear character of the azide group meant that only relatively small interferences between this 1,3-dipole and the adjacent methyl group would occur by rotation (ζ, Figure 1). As anticipated, the analogue **6e** reacted only marginally faster than the mono-methyl derivative **6b** (measured E_{act} 94±10 kJ mol^{-1}), to produce the triazoline **7e**.

A few studies have been made on the related propargyl systems **6f**, **6g**, and **6h**. The linear nature of the acetylene link imparts fewer degrees of freedom compared to the allyl group and although this would be expected to favour the approach of the dipole and dipolarophile, the required transition state for cycloaddition to the triple bond is different to that required by the allyl group. The different frontier orbital situation in changing from the allyl to the propargyl system must also be be taken into account.

The parent (unsubstituted) derivative, **6f**, cycloadded at a faster rate than the corresponding allyl system, **6a**, taking only 2 days at 80° for the disappearance of starting material, to produce the stable cycloadduct triazole **7f** in reasonable yield. As anticipated, the t-butyl azide **6g** could not be isolated pure, the compound undergoing cycloaddition even at room temperature; the cycloadduct **7g** was formed quantitatively within a few hours.

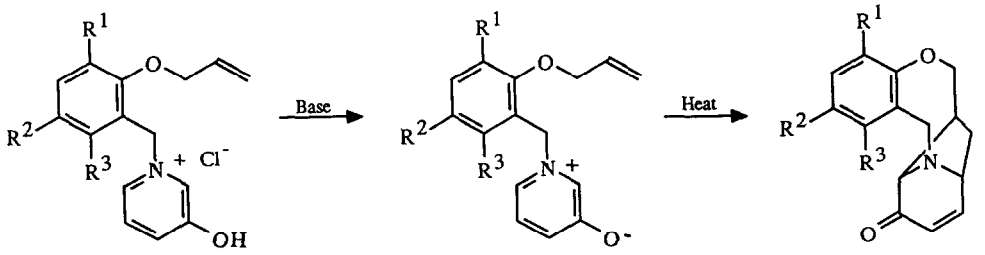
Of particular interest was the behaviour of the dibromide **6h**. This also cycloadded faster than the unsubstituted azide **6f**, reaction being over within 5 h at 80°, to produce the triazole **7h** in quantitative yield. The bromine groups could then be selectively removed, by reduction with tributyltin hydride, to produce the unsubstituted triazole **7f**, albeit in an unoptimised, yield of only 35%. This reaction illustrates the possibility of using appropriate *ortho*-substituents to help accelerate a reaction followed by their removal.

B. 3-Oxidopyridinium Ylides

The second intramolecular cycloaddition studied has been that involving the addition of an alkene across the 2,6-positions of an N-linked 3-oxidopyridinium. Such 1,3-dipolar species are known to react with alkenes in an intramolecular manner, albeit rather sluggishly.[14] Only cycloadditions involving the formation of 6-membered[15] or 5-membered rings[16] have been reported.

The systems examined were prepared in a manner similar to that used to prepare the azides described above, except that the chlorides **5** were reacted with 3-hydroxypyridine, which produced the N-alkylated pyridinium salts **11**. The required ylides, **12**, could be prepared from the pyridinium salts, as required, by treatment with a basic anion exchange resin.

An initial study on the propargyl derivative, **12f** was made but no sign of any intramolecular cycloaddition could be observed. Models show both that the required transition state leading to addition is difficult to assemble in this system and that the expected cycloadduct would be extremely strained by the presence of a bridgehead double bond. Attention was therefore focused on the allyloxy



11 **12** **13**

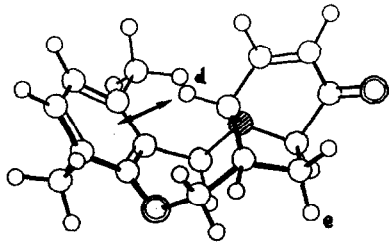
derivatives. The parent system **12a** showed no sign of intramolecular cycloaddition even after heating at 80° for several weeks; ^{1}H n.m.r. spectroscopy indicated a steady degradation of signals of the pyridinium system whilst the vinyl signals remained. Presumably, instead of the intramolecular reaction, side reactions such as intermolecular dimerisations and thermal rearrangement of the allyloxy group took place, leading to a complex array of products. A similar result was obtained with the monomethyl buttress, **12b** but with the much bulkier t-butyl-substituted system, **12c**, some of the required cycloaddition took place (*ca.* 30%). The transition state for cycloaddition with this system is completely different from that required for the dipolar cycloaddition of the corresponding azides, **6**, and, for the t-butyl system **12c**, no large interference between the methylene group of the allyloxy substituent and the t-butyl group appears to be involved in the approach of the dipole to the dipolarophile. The cycloadduct proved to be a mixture of two isomers, **13c**, present in an approximately 40:60 ratio; these two isomers could not be separated by thin layer chromatography and proved to be a mixture of two conformational isomers (*vide infra*).

The 3-oxidopyridinium system also differs from the azide series in that, for cycloaddition, rotation about the ε-bond (Figure 1) is also required in order to properly align the dipole with the dipolarophile. This extra degree of freedom is controllable by the incorporation of a second buttress, as in the dimethyl

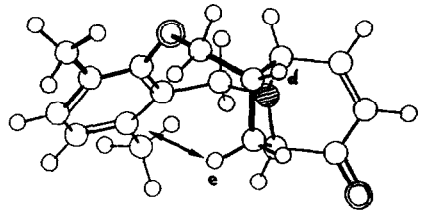
derivative **12e**. As predicted, on heating this compound in benzene at 80°, *a clean cycloaddition reaction occurred within 20 hours to give the corresponding cycloadduct* ***13e*** *in high yield (>80%).* Thus, for this series no cycloaddition proceeds without the assistance of the appropriate steric buttresses. Again, the cycloadduct behaved as a 40:60 mixture of two isomers, which could not be chromatographically separated.

Both the adducts **13c** and **13e** were examined by ^{1}H n.mr. spectroscopy; Table 1 details the results. The gross structure was obtained by analysis of the coupling patterns which indicate that the products are single regio-isomers, the direction of addition being consistent with that obtained in earlier work, *viz.* with the methylene terminus on the olefin dipolarophile adding to position 2 of the oxidopyridinium ring in a stereoselective manner;[15] models indicate that only one approach is sterically possible between the reactants. A clue to the nature of these isomers was given by the fact that, at room temperature, the signals from the dimethyl adduct (**13e**) were broad and sharpened on cooling, whilst heating caused a further broadening of the signals. Molecular models indicate two favourable conformations can exist by flipping of the eight-membered ring. Correlation of these with the existence of the major and minor conformers can be made from the observed chemical shifts. Thus, in the major conformer in the dimethyl series (**13e**), the minor isomer shows the methylene proton, *e* (Figure 4), shielded at δ 1.15 - 1.17, compared to its position in the major conformer, where it appears at δ 2.73 - 2.79, indicating that for the minor conformer (**13e-minor**), the methylene group is folded over the benzene ring. Support for this assignment is gained by the comparative chemical shifts for the bridgehead proton *d*, appears at δ 4.34 in the minor isomer and in a shielded position at δ 3.41 in the major conformer (**13e-major**)(Figure 4), indicating a flipping of the eight-membered ring between the two folded conformers. Similar effects are observed for the t-butyl derivative (**13c**), with the same assignment between the major and minor conformers (no reversal in relative stabilities). For the latter the greater bulk in the steric buttress, the t-butyl group, allows the two conformers to be more stable at room temperature and no line broadening was observed at ambient temperatures.

Figure 4



13e-Major



13e-Minor

Table: ^{1}H Nmr data for the cycloadduct conformers 13c and 13e

*H**	13c-minor	13c-major	13e-minor	13e-major
a	7.8 (dd, 9.5^b, 6.4^d)	7.39(dd 9.5^b, 6.4^d	7.62(dd, 9.5^b, 6.9^d	7.31(dd 9.5^b,6.9^d)
b	5.9 (dd, 9.5^a, 1.2^e)	5.91 (dd 9.5^a, 1.2^e	5.86 (d, 9.5^a)	5.92 (d, 9.5^a)
c	3.84 (broad d, 7.5^e)	3.84 (broad d, 7.3^e)	3.59 (broad d, 7.6^e)	4.03 (broad d, 7.3^e)
d	ca. 4.3	3.84 (broad d, 6.4^e)	4.34 (d, 6.9^e)	3.41 (d, 6.9^e)
e	ca. 1.3	2.16 - 2.18 (m)	1.15 - 1.17 (m)	2.73 - 2.79 (m)
f	1.88(dd, 13.7^a, 9.5^g)	1.74 (dd,13.7^a, 9.5^g)	1.51 (dd, 12.7^a, 9.7^g)	1.83 (dd, 12.7^a, 9.7^g)
g	2.3 - 2.4 (m)	2.3 - 2.4 (m)	2.4 - 2.5 (m)	2.4 - 2.5 (m)
h	4.22(dd, 12.6^i, 1.8^g)	4.11 (dd, 12.6^i, 1.8^g)	4.22 (broad d, 10.7^i	4.11 (broad d, 10.7^i)
i	4.03 (dd, 12.6^h, 2.9^g)	4.02 (dd, 12.6^h, 2.9^g)	4.37 (broad d, 10.7^h)	3.77 (broad d,10.7^h)
j	7.36 (d, 2.5^k)	7.38 (d, 2.5^k)	7.04 (d, 7.8^k)	7.06 (d, 7.8^k)
k	7.05 (d, 2.5^j)	7.09 (d, 2.5^j)	6.86 (d, 7.8^j)	6.90 (d, 7.8^j)
l	3.90 (d, 12.1^m)	3.93 (d, 12.1^m)	4.21 (d, 12.7^m)	4.24 (d, 12.7^m)
m	3.75 (d, 12.1^l)	3.79 (d, 12.1^l)	3.94 (d, 12.7^l)	3.83 (d, 12.7^l)
Me			2.26, 2.33	2.25, 2.32
^{t}Bu	1.40, 1.27	1.41, 1.29		

* See Figure 2 for assignments; superscript letters indicate observed direct couplings. Spectra run at 400MHz in deuteriochloroform.

In conclusion, we have demonstrated that the simple system illustrated in Figure 1 allows one to study the effect of restricting available conformations on the progress of dipolar cycloaddition reactions, a form of conformational analysis.

Acknowledgements
We thank SmithKline Beecham Pharmaceuticals and the SERC for a CASE award (to D. J. W.) and Dr Oliver Howarth, SERC NMR Service, Warwick University, for the high field n.m.r. studies and Dr R. Corbally, Brunel University for the n.m.r. kinetic experiments.

Experimental

Melting points were determined on a hot-stage apparatus and are uncorrected. Mass spectra were recorded on an AEI MS902 spectrometer, infrared spectra on a PE 1420 spectrophotometer on either films or KBr discs. Unless indicated otherwise, ^{1}H N.m.r. spectra were obtained on either a Jeol JNM-FX200 or Varian CFT-20 instrument, using $CDCl_3$ solutions with tetramethylsilane as internal reference. Microanalytical determinations were carried out by MEDAC Ltd, Brunel University. All solvents were distilled before use, using literature procedures.[17] Thin layer chromatography was carried out on 0.25 mm GF60A silica gel plates and column chromatography using Kieselgel 60 silica gel; solvent ratios are in volumes prior to mixing.

General Method for Preparation of aldehydes **2**: To the phenol (5 mmol) in toluene (50 ml) was added tin (IV) chloride (0.55 g, 18 mmol) and tributylamine (3.5 g, 18 mmol). The mixture was stirred at room temperature for 30 min before adding paraformaldehyde (3.7 g, 110 mmol) and heating the mixture to reflux for 16 h. The mixture was cooled, quenched with water (250 ml), acidified to pH2 with conc. HCl, and extracted with chloroform (300 ml). The organic extract was dried, filtered and the solvent removed under reduced pressure. The yellow residue was chromatographed through silica gel, using 1:1 light petroleum - chloroform as eluant to give the required aldehyde.
6-Methyl-2-formylphenol, **2b** (40%), as a pale yellow oil, δ 11.19 (1 H, s), 9.81 (1 H, s), 7.4 - 6.8 (3 H, m), 2.25 (3 H, s). Calcd. for $C_8H_8O_2$ C, 70.59; H, 5.88. found: C, 70.86; H, 6.03%.
4,6-Di-t-butyl-2-formylphenol, **2c** (90%), as a pale yellow solid, m.p. 59°C, δ 11.56 (1 H, s), 9.80 (1 H, s), 7.55 (1 H, d, J, 2.5 Hz), 7.29 (1 H, d, J, 2.5 Hz), 1.42 (9 H, s), 1.32 (9 H, s). Calcd. for $C_{15}H_{12}O_2$: C, 76.92; H, 5.12; found: C, 77.12; H, 5.30%.
3,6-Dimethyl-2-formylphenol, **2e** (40%), as yellow needles, m.p. 53°C, δ 12.08 (1 H, s), 10.22 (1 H, s), 7.22 (1H, d, J7.4Hz), 6.55 (1 H, d, J 7.4 Hz), 2.54 (3 H, s), 2.18 (3 H,s). Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71; found: C, 71.79; H, 6.75%.

Allylation of the Aldehydes **2**[18]: The aldehyde (20 mmol) was dissolved in acetonitrile (100ml) before adding dry potassium carbonate (8 g, 56 mmol and allyl bromide (2.88 g, 24 mmol) and then heating the mixture under reflux for 2 - 12 h, the reactions being monitored by t.l.c. for the disappearance of starting phenol. The mixture was cooled, filtered and the solvent removed under reduced pressure before chromatographing the residue through silica gel, using light petroleum - chloroform mixtures as eluant, to give the allyl ethers.
2-Allyloxybenzaldehyde **3a** (92%), as an oil, δ 10.48 (1 H, s), 6.89 - 7.86 (4 H, m), 5.84 - 6.30 (1 H, m), 5.21 - 5.54 (2 H , m), 4.59 - 4.68 (2 H, m). Calcd. for $C_{10}H_{10}O_2$ C, 74.07; H, 6.17; found: C, 74.22; H, 6.23%.
2-Allyloxy-3-methylbenzaldehyde **3b** (96%), as an oil, δ 10.31 (1 H, s), 7.7 - 6.99 (3 H, m), 6.25 - 5.85 (1 H, m), 5.49 - 5.19 (2 H, m), 4.48 - 4.39 (2 H, m), 2.32 (3 H, s). Calcd. for $C_{11}H_{12}O_2$: C, 75.00; H, 6.82; found: C, 74.83; H, 7.01%.

2-Allyloxy-3,5-di-t-butylbenzaldehyde **3c** (90%) as an oil, δ 10.23 (1 H, s), 7.67 (1 H, d, J, 2.5 Hz), 7.58 (1 H, d, J 2.5 Hz), 5.83 - 6.25 (1 H, m), 5.22 - 5.58 (2 H, m), 4.41 - 4.49 (2 H, m), 1.42 (9 H, m), 1.31 (9 H, m). Calcd. for $C_{18}H_{26}O_2$: C, 78.80; H, 9.40; found: C, 78.63; H, 9.28%.
2-Allyloxy-3,6-dimethylbenzaldehyde **3e** (79%) as an oil, δ 10.48 (1 H, s), 7.24 (1 H, d, J 7.4Hz), 6.85 (1 H, d, J 7.4 Hz), 5.83 - 6.11 (1 H, m), 5.17 - 5.47 (2 H, m), 4.34 - 4.42 (2 H, m), 2.52 (3 H, s), 2.27 (3 H, s). Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42.; found: C, 75.67; H, 7.46%.

2-Propargyloxybenzyl alcohol **4f**: To saligenin (5 g, 40 mmol) in toluene (50 ml) was added K_2CO_3 (5.55 g, 40 mmol) and propargyl bromide (5.94 g as 80% w/w/ soln. in toluene, 40 mmol) and the mixture heated to reflux for 20 h. The mixture was filtered, and the solvent removed under reduced pressure before chromatographing the residue on silica gel, using 93:3 chloroform-methanol as eluant. The ether was obtained as a colourless oil (5 g, 77%), δ6.84 - 7.33 (4 H, m), 4.70 (2 H, d, J 2.5 Hz), 4.67 (2 H, s), 2.49 (1 H, d, J 2.5 Hz), 2.11 - 2.18 (1 H, bs, exch. with D_2O). Calcd. for $C_{10}H_{10}O_2$: C, 74.07; H, 6.17; found: C, 74.30; H, 6.37%.

2-Hydroxy-3,5-dibromobenzyl alcohol: To 3,5-dibromosalicaldehyde (2.5 g, 8.9 mmol) in methanol (50 ml) was added $NaBH_4$ (0.40 g, 10.5 mmol) and the mixture heated to reflux for 2 h. The solvent was removed under reduced pressure and the residue neutralised with dil HCl and extracted with $CHCl_3$, to give the title alcohol as a crystalline solid (2.13 g, 85%), m.p. 86° C, δ 7.55 (1 H, d, J 2.5 Hz), 7.25 (1 H, d, J 2.5 Hz), 6.85 - 7.05 (1 H, bs, exch. D_2O), 4.75 (2 H, s), 2.4 - 2.9 (1 H, bs, exch. D_2O). Calcd. for $C_7H_6Br_2O_2$: C, 29.82; H, 2.15; found: C, 30.01; H, 2.30%.

2-Allyloxy-3,5-dibromobenzyl alcohol **4d**: To 2-hydroxy-3,5-dibromobenzyl alcohol (0.25 g, 0.89 mmol) in MeCN (10 ml) was added K_2CO_3 (0.5 g, 3.6 mmol) and allyl bromide (180 mg, 1.48 mmol) and the mixture heated to reflux for 90 min. The mixture was filtered and the solvent removed under reduced pressure to give the ether as a crystalline solid (207 mg, 72%), m.p. 78-9° C, δ 7.65 (1 H, d, J 2.5 Hz), 7.47 (1 H, d, J 2.5 Hz), 5.95 - 6.20 (1 H, m), 5.20 - 5.51 (2 H, m), 4.65 (2 H, d, J 3.5 Hz), 4.48 (2 H, m), 2.27 (1 H, t, 3.5 Hz). Calcd. for $C_{10}H_{10}Br_2O_2$: C, 37.30; H, 3.13; found: C, 37.55; H, 3.10%.

2-Propargyloxy-3,5-dibromobenzyl alcohol **4h**: To 2-hydroxy-3,5-dibromobenzyl alcohol (0.5 g, 1.77 mmol) in toluene (30 ml) was added K_2CO_3 (1 g, 7.2 mmol) and propargyl bromide (0.32 g, 2.1 mmol, as 80% w/wsolution in toluene) and the mixture heated to reflux for 16 h. The mixture was filtered and the solvent removed *in vacuo* to give a crystalline product (0.52 g, 92%), m.p. 108°C, δ 7.65 (1 H, d, J 2.5 Hz), 7.53 (1 H, d, J 2.5 Hz), 4.67 - 4.83 (4 H, m), 2.57 (1 H, m), 2.15 (1 H, bs, exch. D_2O). Calcd. for $C_{10}H_8Br_2O_2$: C, 37.54; H, 2.52; found: C, C, 37.31; H, 2.34%.

2-Propargyloxy-3,5-di-t-butylbenzyl alcohol **4g**: The aldehyde **2c** (3 g, 12.8 mmol) in acetone (50 ml) was treated with K_2CO_3 (9 g, 65 mmol) and propargyl bromide (2.07 g, 14 mmol; 80% w/w solution in toluene) and the mixture heated at reflux fo 12 h. The mixture was filtered, the solvent removed *in vacuo* and the residue chromatographed through silica gel, using 1:1 chloroform - light petroleum as eluant., to give the aldehyde **3g** (2.5 g, 71%) as an oil; δ 10.32 (1 H, s), 7.67 (1 H, d, J 2.5 Hz), 7.59 (1 H, J 2.5 Hz), 4.59 (2 H, d, J 2.5 Hz), 2.49 (1 H, t, J 2.5 Hz), 1.44 (9 H, s), 1.32 (9 H, s). Calcd. for. $C_{18}H_{24}O_2$: C, 79.41; H, 8.82; found: C, 79.56; H, 9.03%.
Reduction of the aldehyde **3g** (0.89 g, 3.3 mmol) was achieved with $NaBH_4$ in the manner described below
to give the title alcohol (0.81 g, 91%), as an oil; δ7.2-7.29 (2 H, m), 4.74 (2 H, s), 4.56 (2 H, d, J 2.5 Hz), 2.55 (1 H, t, J 2.5 Hz), 1.41 (18 H, s), 1.29 -1.36 (1 H, bs, exch. D_2O).Calcd. for $C_{18}H_{26}O_2$: C, 78.83; H, 9.49; found: C, C,78.99; H, 9.69%.

Reduction of the Aldehydes **3**: The aldehyde (10 mmol) in methanol (50 ml) was treated with $NaBH_4$ (0.78 g, 20 mmol) at room temperature for 1 h before removing the solvent *in vacuo* adding water (30

ml) and extracting with chloroform (30 ml). The extract was dried, filtered and the solvent removed prior to chromatography through silica gel, using methanol-chloroform mixtures as eluant, to afford the product alcohols.

2-Allyloxybenzyl alcohol **4a:** (90%) as a mobile oil, δ 6.78 - 7.43 (4 H, m), 5.81 - 6.28 (1 H, m), 5.18 - 5.51 (2 H, m), 4.68 (2 H, s), 4.50 - 4.60 (2 H, m), 2.18 - 2.40 (1 H, bs, exch. D_2O).
2-Allyloxy-3-methylbenzyl alcohol **4b**: (72%), as an oil, δ 6.96 - 7.22 (3 H, m), 5.86 - 6.05 (1H, m), 5.17 - 5.49 (2 H. m), 4.67 (2 H, s), 4.31 - 4. 41 (2 H, m), 2.28 (3 H, s). Calcd. for $C_{11}H_{14}O_2$: C, 74.16; H, 7.87; found: C, 74.42;, H, 8.07%.
2-Allyloxy-3,5-di-t-butylbenzyl alcohol **4c**: (99%), m.p. 45°C, δ 7.27 (1 H, d, J 2.5 Hz), 7.22 (1 H, d, J 2.5 Hz), 5.86 - 6.26 (1 H, m), 5.15 - 5.57 (2 H, m), 4.69 (2 H, m), 4.35 - 4.45 (2 H, m), 1.53 - 1.86 (1 H, bs, exch. D_2O), 1.39 (9 H, s), 1.30 (9 H, s). Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21; found: C, 78.44; H, 10.39%.
2-Allyloxy-3,6-dimethylbenzyl alcohol **4e**: (80%), as an oil, δ 7.00 (1 H, d, J 7.4 Hz), 6.81 (1 H, d, J 7.4 Hz), 5.87 - 6.28 (1 H, m), 5.16 - 5.52 (2 H, m), 4.70 (2 H, s), 4.30 - 4.40 (2 H, m), 2.35 (3 H, s), 2.24 (3 H, s), 2.11 (1 H, bs, exch. D_2O). Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; found: C, 74.75; H, 8.51%.

Preparation of the Chlorides **5**[19]: To a stirred solution of oxalyl chloride (5 mmol) in dichloromethane (35 ml) at 0°C was added, dropwise, dimethylformamide (0.36 g, 5 mmol). To the cooled mixture was then added the alcohol, **4** (4 mmol) and the mixture heated to reflux for 2 h. The solvent was removed *in vacuo*, and the residue rapidly chromatographed through silica gel, using light petroleum - chloroform as eluant, to afford the title compounds.
2-Allyloxybenzyl chloride **5a**: 82%, as an oil, δ 6.79 - 7.38 (4 H, m), 5.83 - 6.10 (1 H, m), 5.16 - 5.54 (2 H, m), 4.65 (2 H, m), 4.53 - 4.62 (2 H, m). Calcd. for $C_{10}H_{11}OCl$: C, 65.93; H, 6.04; found: C, 66.10, H, 6.30%.
2-Allyloxy-3-methylbenzyl chloride **5b**: 72%, as an oil, δ 6.97 - 7.27 (3 H, m), 5.88 - 6.16 (1 H, m), 5.18 - 5.53 (2 H, m), 4.63 (2 H, s), 4.36 - 4.45 (2 H, m), 2.29 (3 H, s).
2-Allyloxy-3,5-di-t-butylbenzyl chloride **5c**: 42%, m.p. 48°C, δ 7.21 - 7.31 (2 H, overlapping dd, J 2.5 Hz),5.85 - 6.21 (1 H, m), 5.06 - 5.61 (2 H, m), 4.61 (" H, s), 4.39 - 4.59 (2 H, m), 1.39 (9 H, s), 1.30 (9 H, s). Calcd. for $C_{18}H_{22}OCl$: C, 73.32; H, 9.23; found: C, 73.39, H, 9.22%.
2-Allyloxy-3,5-dibromobenzyl chloride **5d**: 58%, m.p. 71°C, δ 7.61 (1 H, d, J 2.5 Hz), 7.44 (1 H, d, 2.5Hz), 5.98 - 6.17 (1 H, m), 5.18 - 5.49 (2 H, m), 4.52 (2 H, s), 4.50 (2 H, m). Calcd. for $C_{10}H_9Br_2OCl$: C, 35.39; H, 2.65; found: C, 35.52; H, 2.83%.
2-Allyloxy-3,6-dimethylbenzyl chloride: **5e**: 62%, as an oil, δ7.00 (1 H, d, J 7.4 Hz), 6.81 (1 H, d, J 7.4 Hz), 5.89 - 6.30 (1 H, m), 5.16 - 5.56 (2 H, m), 4.71 (2 H, s), 4.36 - 4.46 (2 H, m), 2.38 (3 H, s), 2.24 (3 H, s). Calcd. for $C_{12}H_{15}OCl$: C, 68.39; H, 7.17; found: C, 68.51; H, 7.17%.
2-Propargyloxybenzyl chloride **5f**: 89%, as an oil, δ6.93 - 7.30 (4 H, m), 4.74 (2 H, d, J 2.5 Hz), 4.63 (2 H, s), 2.49 (1 H, t, J 2.5 Hz). Calcd. for $C_{10}H_9OCl$: C, 66.66; H, 5.00; found: C,66.75; H, 5.23%.
2-Propargyloxy-3,5-di-t-butylbenzyl chloride **5g**: 80%, δ 7.17 - 7.27 (2 H, m), 4.68 (2 H, s), 4.60 (2 H, d, J 2.5 Hz), 2.58 (1 H, t, J 2.5 Hz), 1.41 (9 H, s), 1.29 (9 H, s).
2-Propargyloxy-3,5-dibromobenzyl chloride **5h**: 88%, m.p. 76°C, δ 7.69 (1 H, d, J 2.5 Hz), 7.55 (1 H, d, J 2.5 Hz), 4.82 (2 H, d, J 2.4 Hz), 4.71 (2 H, s), 2.59 (1 H, t, J 2.4 Hz). Calcd. for $C_{10}H_7OBr_2Cl$: C, 35.49; H, 2.08; found: C, 35.42; H, 2.07%.

Preparation of the Azides **6**[20] : To a solution of sodium azide (393 mg, 6 mmol) in dry dimethyl sulphoxide (30 ml) was added the chloride (5.5 mmol) and the solution stirred at room temperature for 24 h before adding water (60 ml) and extracting with $CHCl_3$ (50 ml). The solvent was removed *in vacuo* and the residue purified by rapid column chromatography through silica gel, using 60:40 $CHCl_3$-light petroleum as eluant. The isolated azides were generally prepared immediately prior to use and stored until required at -10°C.

2-Allyloxybenzyl azide **6a**: 73%, as an oil, δ 6.79 - 7.34 (4 H, m), 5.80 - 6.22 (1 H, m), 5.16 - 5.50 (2 H, m), 4.51 - 4.60 (2 H, m), 4.36 (2 H, s). Calcd. for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21; found: C, 63.55; H, 5.99; N, 21.98%.
2-Allyloxy-3-methylbenzyl azide **6b**: 71%, as an oil, δ 6.98 - 7.20 (3 H, m), 5.85 - 6.13 (1 H, m), 5.17 - 5.53 (2 H, m), 4.29 - 4.46 (2 H, m), 4.36 (2 H, s), 2.29 (3 H, s). Calcd. for $C_{11}H_{13}N_3O$: C, 65.02; H, 6.40; N, 20.69; found: C, 65.37; H, 6.63; N, 20.85%.
2-Allyloxy-3,5-di-t-butylbenzyl azide **6c**: 83%, as an oil; δ 7.31 (1 H, d, J 2.5 Hz), 7.14 (1 H, d, J 2.5 Hz), 5.85 - 6.21 (1 H, m), 5.15 - 5.55 (2 H, m), 4.38 - 4.42 (2 H, m), 4.35 (2 H, s), 1.39 (9 H, s), 1.31 (9 H, s). Calcd. for $C_{18}H_{27}N_3O$: C, 71.72; H, 9.03:, N, 13.94; found: C, 72.02; H, 9.28; N, 14.06%.
2-Allyloxy-3,5-dibromobenzyl azide **6d**: 100%, as an oil; δ.71 (1 H, d, J 2.5Hz), 7.47 (1 H, d, J 2.5 Hz), 6.01 - 6.21 (1 H, m), 5.32 - 5.55 (2 H, m), 4,.50 (2 H, m), 4.42 (2 H, s). Calcd. for $C_{10}H_9N_3OBr_2$: C, 34.58; H, 2.59; N, 12.10; found: C, 34.73; H, 2.69; N, 12.35%.
2-Allyloxy-3,6-dimethylbenzyl azide **6e**: 96%, as an oil, δ 7.00 (1 H, d, J 7.4 Hz), 6.84 (1 H, d, J 7.4 Hz), 5.86 - 6.27 (1 H, m), 5.18- 5.55 (2 H, m), 4.43 (2 H, s), 4.27 - 4.37 (2 H, m), 2.33 (3 H, s), 2.26 (3 H, s). Calcd. for $C_{12}H_{15}N_3O$: C, 66.36; H, 6.91; N, 19.35; found: C, 66.59; H, 7.13; N, 19.63%.
2-Propargyloxybenzyl azide **6f**: 96%, as an oil, δ 6.84 - 7.33 (4 H, m), 4.72 (2 H, d, J 2.5 Hz), 4.35 9(2 H, s), 2.49 (1 H, t, J 2.5 Hz)
2-Propargyloxy-3,5-di-t-butylbenzyl azide **6g**: 80%, as an oil, δ7.36 - 7.16 (2 H, m, masked by cycloadduct signals), 4.52 (2 H, d, 2.5 Hz), 4.42 (2 H, s), 2.55 (1 H, t, J 2.5 Hz), 1.41 (9 H, s), 1.29 (9 H, s). The compound was unstable, with respect to intramolecular cycloaddition.
2-Propargyloxy-3,5-dibromobenzyl azide **6h**: 100%, m.p. 84°C, δ 7.69 (1 H, d, J 2.5 Hz), 7.55 (1 H, d, J 2.5 Hz), 4.79 (2 H, d, J 2.4 Hz), 4.54 (2 H, s), 2.59 (1 H, t, J 2.4 Hz). Found: m/z 344; calcd. for $C_{10}H_7N_3Br_2O$ $M^{+\cdot}$ 344.

Kinetic Studies on the Cyclisation of the Azides **6**
Samples of the freshly prepared azides (ca. 50 mg) in deuterochloroform (0.5 ml) were sealed in 2.5mm standard n.m.r tubes under a reduced atmosphere. Duplicate runs were carried out on the selected azides using a range of at least 4 different temperatures in the range 30 -70°C. The progress of the reactions was monitored by n.m.r, using a JEOL FX 200 instrument, fitted with a variable temperature probe, using integrations of key signals appearing in the product and disappearing with the starting material. First order reaction rates were assumed for the cycloadditions.

Preparation of the Triazoline and Triazole Cycloadducts: The azide (2 mmol) in AR grade benzene (20 ml) was heated at reflux for 5h - 7 days, as required from the n.m.r. monitoring studies. The solvent was removed *in vacuo* and the residue collected and dried in a drying pistol to remove all residual solvent. The products were not chromatographed, since this lead to extensive decomposition. Where possible the products were recrystallised from MeOH - light petroleum - ether mixtures.
Triazolines:
7a: 50% (after recrystallisation); m.p. 55°C; δ (400 MHz) 7.24 (1 H, dd, J 1.2, 8.1 Hz), 7.16 (1 H, ddd, J 7.4, 6.2, 1.2 Hz), 7.00 (1 H, ddd, J 7.4, 6.2, 1.2Hz), 6.93 (1H, dd, J 8.0, 1.2 Hz), 5.17 (1H, d, J 16.0 Hz), 4.77 (1 H, d, J 16 Hz), 4.17 (1 H, dd, J 12.6, 3.3 Hz), 4.15 (1 H, dd, J 16.2, 10.9 Hz), 3.99 (1 H, dd, J 16.2, 10.9 Hz), 3.85 (1 H, m), 3.50 (1 H, dd, J 12.6, 7.8 Hz). Calcd. for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.87; N, 22.21; found: C, 63.21; H, 5.86; N, 22.33%.
7b: 100%; as an oil; δ 6.88 - 7.21 (3 H, m), 5.15 (1 H, d, J 15.6 Hz), 4.73 (1 H, d, J 15.6 Hz), 3.25 - 4.29 (5 H, m), 2.18 (3 H, s). Calcd. for $C_{11}H_{13}N_3O$: C, 65.02; H, 6.40; N, 20.69; found: C,65.26; H, 6.48; N, 21.01%.
7c: 100%; m.p. 162°C; δ 7.25 (1 H, d, J 2.5 Hz), 7.19 (1 H, d, J 2.5 Hz), 5.14 (1 H, d, J 15.6 Hz), 4.81 (1 H, d, J 15.6 Hz), 3.88 - 4.14 (4 H, m), 3.23 - 3.34 (1 H, m), 1.35 (9 H, s), 1.30 (9 H, s). Calc. for $C_{18}H_{27}N_3O$: C, 71.72; H, 9.03; N, 13.94; found: C, 72.02; H, 9.32; N, 13.65%.
7d: 100%; m.p. 110°C; δ 7.62 (1 H, d, J 2.5 Hz), 7.39 (1 H, d, J 2.5 Hz), 5.15 (1 H, d, J 15.6 Hz), 4.80

(1 H, d, J 15.6 Hz), 3.89 - 4.33 (4 H, m), 3.44 - 3.48 (1 H, m). Calcd. for $C_{10}H_9N_3Br_2O$: $M^{+\cdot}$ 344.9113; found m/z 344.9113.
7e: 100%, as an oil; δ 6.82 (1 H, d, J 7.4 Hz), 6.67 (1 H, d J 7.4 Hz), 5.30 (1 H, d, J 16 Hz), 4.20 (1 H, d, J 16 Hz), 3.51 (1 H, dd, J, 16, 10.3 Hz), 3.40 (1 H, dd, J 12.4, 3.9 Hz), 3.35 (1 H, dd, J 16, 5.4 Hz), 3.09 - 3.15 (1 H, m), 2.73 (1 H, dd, J 12.4, 9.3 Hz), 2.17 (3 H, s), 2.12 (3 H, s). Calcd. for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34; found: C, 66.16; H, 6.98; N, 19.18%.
Triazoles:
7f: 90%; m.p. 122°C; δ5.51 (1 H, s), 6.91 - 7.34 (4 H, m), 5.69 (2 H, s), 5.32 (2 H, s). Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45; found: C, 63.95; H, 5.01; N, 22.29%.
7g: 100%; m.p.133°C, δ 7.39 (1 H, s), 7.35 - 7.15 (2 H, m), 5.56 (2 H, s), 5.21 (2 H, s), 1.43 (9 H, s), 1.30 (9 H, s). Calcd. for $C_{18}H_{25}N_3O$: C, 72.24; H,8.36; N, 14.05; found: C, 72.64; H, 8.43; N, 14.28%.
7h: 88%; m.p. 204-205°C; δ (250 MHz, D_6-DMSO) 7.92 (1 H, d, J 2.5 Hz), 7.86 (1 H, d, J 2.5 Hz), 7.73 (1 H, s), 5.89 (2 H, s), 5.51 (2 H, s). Calcd. for $C_{10}H_7N_3Br_2O$: C, 34.81; H, 2.05; N, 12.18; found: C, 34.94; H, 2.29; N, 12.00%.

Debromination[21] *of the Dibrominated triazole* **7h**: To the triazole (40 mg, 0.16 mmol) in toluene (15 ml) was added tri-n-butyltin hydride (337 mg, 16 mmol) and azobisisobutyronitrile (1 mg). The solution was heated at reflux for 16 h, the solvent removed *in vacuo* and the residue then purified by preparative t.l.c. to give the debrominated triazole, **7e** (8 mg, 35%), m.p. and mixed m.p. 122°C, identical t.l.c.behaviour and ^{1}H n.m.r. spectra.

Preparation of 3-Oxidopyridinium Ylides: The halide **5** (2 mmol) was added to a stirred solution of 3-hydroxypyridine (2 mmol) in acetonitrile (50 ml) for 12 h. The solvent was removed *in vacuo* and the crystalline residue triturated with ether before collecting and drying to afford the product N-substituted 3-hydroxypyridinium chloride **10**. The corresponding betaines, **12** were prepared by dissolving the chloride salt **11** (0.5 mmol) in THF (30 ml) and stirring with Amberlite 401 ion exchange resin [2 g, activated before use by sequential washing with 4N NaOH (200 ml), water (250 ml) and acetone (250 ml)] for 4 h at room temperature before removing the resin by filtration and evaporation of the solvent. The 3-oxidopyridinium betaines **12** were used directly in cycloaddition studies without further purification.
11a: 80%; m.p. 198°C; δ (D_6DMSO) 7.76 - 8.61 (5 H, m), 6.90 - 7.53 (4 H, m), 5.2 - 6.02 (3 H, m), 5.22 - 5.30 (2 H, m), 4.51 - 4.60 (2 H, m). Calcd. for $C_{15}H_{16}NO_2Cl$: C, 64.85; H, 5.81; N, 5.04; found: C, 64.65; H, 5.89; N, 4.91%.
11c: 70%; m.p.203°C; δ 7.89 - 8.49 (5 H, m), 7.42 (1 H, d J 2.5Hz), 7.18 (1 H, d, J 2.5 Hz), 6.01 -6.20 (1 H, m), 5.79 (2 H, s), 5.27 - 5.47 (2 H, m), 4.41 - 4.43 (2 H, m), 1.36 (9 H, s), 1.25 (9 H, s). Calcd. for $C_{23}H_{32}NO_2Cl$: C, 70.84; H, 8.27; N, 3.59; found: C, 70.58; H, 8.04; N, 3.67%.1
11e: 55%; m.p. 173°C; δ 9.07 (1 H, s), 8.14 (1 H, dd, J 8.8, 1.2 Hz), 7.90 (1 H, d, J 5.5 Hz)
7.22 (1 H, d J 7.4 Hz), 6.99 (1 H, d, J 7.4 Hz), 5.96 - 6.15 (1 H, m), 5.73 (2 H, s), 5.27 - 5.43 (2 H, m), 4.35 - 4.38 (2 H, m), 2.38 (3 H, s), 2.31 (3 H, s). Calcd. for $C_{17}H_{20}NO_3Cl$: C, 67.21; H, 6.64; N, 9.22; found: C, 67.50; H, 6.64; N, 9.47%.

Cycloaddition studies on the Betaines **12a**, **12c** *and* **12e**: The betaines (50 mg) were dissolved in D_6-benzene (0.5 ml) and sealed *in vacuo* in 5mm n.m.r. tubes. The tubes were heated to 95°C and the reactions monitored at intervals by ^{1}H n.m.r. spectroscopy.
12a: No intramolecular cycloaddition was observed after 10 days heating, as indicated by the retention of the allyloxy group protons. T.l.c. examination of the reaction product showed no starting material remained.
12c: After heating this betaine for 7 days at 95°C, no starting material was detected. The product was subjected to preparative t.l.c., using 98:2 chloroform-methanol as eluant, to afford the cycloadducts as an off-white solid (16 mg, 32%). ^{1}H N.m.r. indicated this was a mixture of two conformers; see Table 1. Calcd. for $C_{23}H_{31}NO_2$: C, 78.15; H, 8.84; N, 3.96; found: C, 78.23; H, 8.74; N, 3.63%.

12e: The betaine was heated for 20 h, after which time all starting material had disappeared. After removal of the solvent the residue was chromatographed through a short column of silica gel, using chloroform as eluant, to give the cycloadduct (100 %), identified as a mixture of conformers from its ^{1}H n.m.r. spectrum; see Table 1. Calcd. for $C_{17}H_{19}NO_2.H^+$ MH^+:270.1494; found: m/z 270.1513.

References and Notes

1. N. S. Isaacs, 'Liquid Phase High Pressure Chemistry', J. Wiley & Sons, Chichester, 1981, ch.4.
2. C. W. Bird, D. L. Colinese, R. C. Cookson, J. Hudec and R. D. Williams, *Tetrahedron Lett.*, 373 (1961); G. N. Schrauzer and S. Eichler, *Chem. Ber.*, **95**, 2764 (1962); F. D. Mango, *Tetrahedron Lett.*, 1509 (1973).
3. L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis', Wiley Interscience, New York, 1973 pp. 236 - 243.
4. N. D. Epiotis, *J. Amer. Chem. Soc.*, **95**, 1200 (2973); J. Sauer and R. Sustmann, *Angew. Chem. Int. Edn.(Eng)*, **19**, 779 (1980).
5. N. L. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960); J. Dale, *J. Chem. Soc.*, 93 (1963);Y. Ito and T. Matsuura, *J. Amer. Chem. Soc.*, **195**, 5237 (1983); G. Coll, A. Costa, P. M. Deya, F. Flexas, C. Rotger and J. M. Saa, *J. Org. Chem.*, **57**, 6223, (1992). For an example in cycloadditions reactions see R. K. Boeckman and S. S. Ko, *J. Amer. Chem. Soc.*,**104**, 1033 (1982).
6. M. I. Page and W. P. Jencks, *Proc. Nat. Acad. Sci. U.S.A.*, **68**, 1678-1683 (1971). For an example in intramolecular cycloaddition see H. W. Gschwend, *et al.*, *J. Org. Chem.*, **38**, 2169 (1973).
7. Calculated using the Chem-X suite of programs.
8. R. Fusco, L. Garanti and G. Zecchi, *J. Org. Chem.*, **40**, 1906 (1975).
9. G. Casiraghi, G. Casnati, G. Puglia, G. Sartori and G. Terenghi, *J.Chem.Soc. Perkin Trans. 1*, 1862 (1980).
10. Kindly provided by Dr Oliver Howarth, SERC High Field NMR Laboratory, Department of Chemistry, University of Warwick, Coventry, U.K.
11. We thank Dr J. J. Gosper for his help with these calculations.
12. A. Fersht, 'Enzyme Structure and Mechanism', W. F. Freeman and Co. Ltd., Reading, pp. 274 - 287 and refs. cited therein.
13. See B. Nilsson, P. Martinson, K. Olsson and R. E. Carter, *J. Amer. Chem. Soc.*, **96**, 3190 (1974) and references cited therein.
14. P. G. Sammes, *Gazz. Chim. Italiana*, **116**, 109 (1986).
15. S. M. Bromidge, D. A. Archer and P. G. Sammes, *J. Chem. Soc. Perkin Trans. 1*, 313 (1990).
16. R. A. Joshi, and T. Ravindranathan, *Indian J. Chem., Sect. B*, **23**, 300 (1984).
17. D. D. Perrin, W. L. F. Amarego and D. R. Perrin, 'Purification of Laboratory Chemicals', Pergamon Press, Oxford, 1966.
18. C. A. Burkhard, J. V. Schmitz and R. E. Burnett, *J. Amer. Chem. Soc.*, **75**, 5957 (1953).
19. R. E. Ireland, D. W. Norbeck, G. S. Mandel and N. S. Mandel, *J. Amer. Chem. Soc.*, **107**, 3285 (1985).
20. S. Kulstad and L. A. Malmsten, *Acta Chim. Scand.*, **B33**, 469 (1979).
21. J. M. Berge and S. M. Roberts, *Synthesis*, 471 (1979).