Use of Steric Buttresses to enhance Intramolecular Cycloadditions

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Examples are given illustrating the use of *ortho*-substituents on substituted benzene rings as steric buttresses to limit the conformational space available to a dipole and dipolarophile, forcing them into closer proximity and hence to allow cycloadditions to proceed that otherwise do not.

The rate of cycloaddition of, for example, 1,3-dipoles to dipolarophiles can be accelerated by increasing the frequency rate of encounter of the reactants. Steric buttressing can be used for this purpose by reducing the available conformational space to the reactants and we have recently reported on the acceleration of a cycloaddition reaction in the presence of steric buttresses.[1]

We report here two examples of reactions which only proceed in the presence of suitable buttresses. Thus, *N*-(2-allyloxy)benzyl-3-oxidopyridinium betaine 1 does not give any cycloadducts of the type 5 when heated for 7 days in deuteriobenzene solution at temperatures of ⩾ 80 °C; only a slow, general decomposition of the betaine is observed, ascribed to side reactions such as dimerisation of the betaine system[2] and rearrangement of the allyloxy substituent. This is not altogether surprising since the product requires the dipolarophile and dipole to meet with formation of an eight-membered ring. Despite the copious literature dealing with intermolecular cycloadditions of 3-oxidopyridinium betaines to multiple bonds,[3] relatively few intramolecular examples have been reported. In 1976 we observed the intramolecular cycloaddition of substituted betaines to give tricyclic adducts *via* the formation of a six-membered ring[4] but attempts to make larger ring systems failed. Joshi and Ravindranathan have also prepared a number of intramolecular cycloadducts starting with *N*-homoallylpyridine betaines involving formation of a five-membered ring.[5] In these intramolecular examples the rate of cycloaddition across the unactivated olefin was often sluggish, owing to the poor HOMO–LUMO interactions.

By incorporating a sterically bulky group *ortho* to the allyloxy dipolarophile, we envisaged that the dipolarophile's allowed conformational space would be significantly reduced.[1] In this manner the frequency of encounter of the dipolarophile with the dipole would be considerably favoured and reaction enhanced. A study of the monomethyl derivative 2 again failed to produce any cycloadduct, suggesting the need

for a bulkier (more restrictive) buttressing effect. The di-*tert*-butyl derivative 3 was prepared. After heating the betaine 3 for 5 days in benzene at reflux, all the starting material had disappeared and the only product that could be isolated was the expected cycloadduct 6, albeit in modest yield (15%). ^{1}H NMR spectroscopy indicated that the product was formed regioselectively, but as a 40:60 mixture of two conformational isomers (*vide infra*).† That the product was a cycloadduct was indicated by the characteristic ^{1}H NMR signals, especially of the enone system[4] and the disappearance of the allyl signals.

Although the single buttressing effect of the *tert*-butyl group had allowed us to observe the new cycloaddition process the low yield and long reaction time suggested that side reactions were still competing. This prompted us to study the effect of a buttress on both sides of the reacting dipole and dipolarophile. The 3,6-dimethyl analogue 4 was therefore prepared; it was expected that the 6-methyl group would significantly restrict the conformational space available to the bulky 3-oxidopyridinium betaine, whilst the 3-methyl group would likewise restrict the available conformational space of the allyloxy group, thus holding the two components in the close proximity (see Fig. 1). Heating the betaine 4 for 20 h in refluxing benzene smoothly produced the cycloadduct 7, again as a 40:60 mixture of conformers, in over 80% isolated yield.

A detailed ^{1}H NMR examination of the cycloadducts 6 and 7 showed they had the same pattern of proton couplings, consistent with the regiospecific addition of the methylene terminus of the alkene to position 2 of the pyridinium heterocycle, in accordance with previous observations.[4] Variable temperature studies showed the conformers were interconvertible, compound 6 showing broadening of the signals at room temperature whilst compound 7 needed a higher temperature for coalescence to occur; the major isomer was assigned structure A and the minor isomer structure B (Fig. 2),
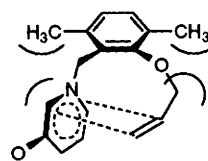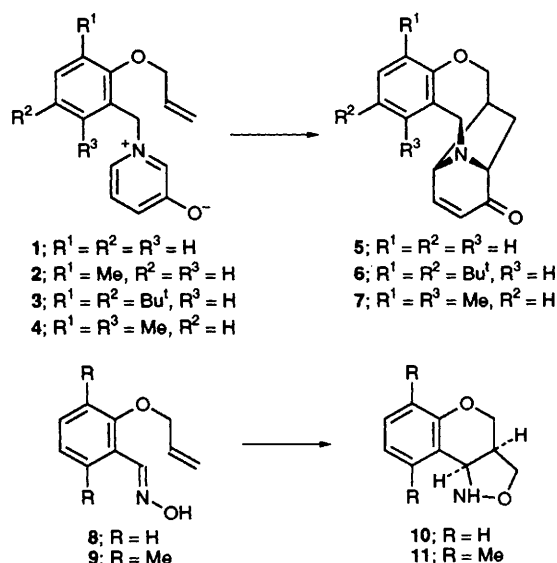
1; R¹ = R² = R³ = H
2; R¹ = Me, R² = R³ = H
3; R¹ = R² = Buᵗ, R³ = H
4; R¹ = R³ = Me, R² = H

5; R¹ = R² = R³ = H
6; R¹ = R² = Buᵗ, R³ = H
7; R¹ = R³ = Me, R² = H

8; R = H
9; R = Me

10; R = H
11; R = Me

Fig. 1 Proposed transition state for the cycloaddition of 4

A   B
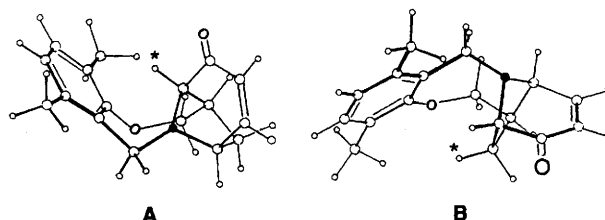
Fig. 2 Structures of the major (A) and minor (B) conformers of 7

† All new compounds were identified by microanalysis and/or accurate mass measurements.

the indicated protons (*) showing shielding by the aromatic ring.‡

A further example of steric enhancement of cycloaddition utilised the oximes **8** and **9**. Grigg *et al.* have studied the cycloaddition of compound **8** as a putative 1,3-dipole, as its nitrone tautomer.[6] However, he found that the oxime **8** did not give the cycloadduct **10** after prolonged heating at 140 °C, although Oppolzer and Keller[7] have reported signs of cycloaddition, to give low yields of compounds **10**, by heating in toluene at 110 °C for 20 h.

In our hands, no change occurred when the oxime **8** was heated at 110 °C for 20 h; it was completely unaffected by heating at 80 °C in benzene for 2 days. In complete contrast, under the same conditions, the substituted oxime **9**, m.p. 50–51 °C, was quantitatively converted into the isoxazolidine **11**, m.p. 80–81 °C. A detailed ^{1}H NMR examination revealed that the cycloaddition had occurred regiospecifically; no evidence was found for the formation of any regioisomer.

These examples of striking differences in reactivity demonstrate the generality of the use of steric buttresses to accelerate reactions that otherwise do not proceed easily, thus opening up entry to a range of novel structures.

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