Steric Acceleration of Intramolecular Azide Cycloadditions

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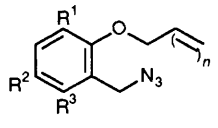
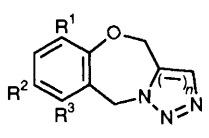
Use of conformational restraints, induced by different *ortho*-substituents in 1-allyloxy- and 1-prop-2-ynyloxy-2-azidomethylbenzenes, can be employed to enhance the smooth intramolecular addition of the azide group to the unsaturated bond, followed by, in one example, removal of the conformational constraint.

The steric effects of *ortho*-substituents in aromatic systems have been studied in a wide range of ionic reactions[1] but, although conformational restraints, such as the Thorpe–Ingold effect[2] are well known in favouring ring formation and the '*gem*-dimethyl' effect in assisting cyclisations,[3] few studies have focused on the *ortho*-substituent effect in cycloaddition reactions. An exception is on the photochemical behaviour of *ortho*-substituted aromatic aldehydes and ketones, where steric effects can be used to favour the formation of benzocyclobutenes.[4] Herein we report some studies on the intramolecular cyclisation of the azides related to compound **1**.

The dipolar character of the azido group enables it to undergo 1,3-dipolar cycloadditions with olefins[5] forming dihydro-1,2,3-triazoles in a concerted, stereospecific manner with the olefin geometry preserved in the cycloadduct. Similarly, the reaction with acetylenes yields 1,2,3-triazoles. Although the product dihydrotriazoles and triazoles have considerable synthetic potential, the rate of such cycloadditions can be sluggish, requiring prolonged reaction times, and thermal decomposition of the starting azide group can compete with cycloaddition. Furthermore, the product dihydrotriazoles are often thermally unstable, undergoing degradation, for example to aziridines or imines.

Our initial aim was to extend the work of Fusco *et al.*[6] on the cycloaddition of 1-allyloxy-2-azidobenzene in order to obtain a novel series of heterocyclic compounds. The azides **1–7** were freshly prepared, as required, by standard chemical routes starting from the parent phenols. We had hoped that the presence of the benzene ring would ensure sufficient restraint on the available conformational degrees of free rotation to allow formation of the fused, seven membered oxazepine ring. In the event, compound **1** underwent only a slow cycloaddition reaction and, in refluxing benzene, the reaction took over 7 days to form the expected dihydrotriazole product **8**.† Attempts to speed up the reaction by heating at higher temperatures gave rise to degradation of the azide and reduced yields of the product. In order to increase the rate of cycloaddition, substituents were introduced *ortho* to the allyloxy group. Modelling studies (using the CHEM-X suite of programs) showed that these should reduce the conformationally allowed space occupied by the allyl group, hence forcing it nearer to the azide dipole.





1; $R^1 = R^2 = R^3 = H$, $n = 1$
2; $R^1 = Me$, $R^2 = R^3 = H$, $n = 1$
3; $R^1 = R^2 = Br$, $R^3 = H$, $n = 1$
4; $R^1 = R^2 = Bu^t$, $R^3 = H$, $n = 1$
5; $R^1 = R^3 = Me$, $R^2 = H$, $n = 1$
6; $R^1 = R^2 = R^3 = H$, $n = 2$
7; $R^1 = R^2 = Br$, $R^3 = H$, $n = 2$

8; $R^1 = R^2 = R^3 = H$, $n = 0$
9; $R^1 = Me$, $R^2 = R^3 = H$, $n = 0$
10; $R^1 = R^2 = Br$, $R^3 = H$, $n = 0$
11; $R^1 = R^2 = Bu^t$, $R^3 = H$, $n = 0$
12; $R^1 = R^3 = Me$, $R^2 = H$, $n = 1$
13; $R^1 = R^2 = R^3 = H$, $n = 1$
14; $R^1 = R^2 = Br$, $R^3 = H$, $n = 1$

† All new compounds have been fully characterised by either microanalysis or accurate mass measurements.

As expected, the methyl derivative **2** reacted much faster, cycloaddition to give compound **9** being complete within 10 h in refluxing benzene, showing an activation energy of 123 kJ mol^{-1}. The bromide **3** (the bromo group being approximately isosteric to a methyl substituent) also reacted more rapidly than either the unsubstituted system or the methylated analogue, to produce adduct **10**. The increase in the rate of reaction of the bromo derivative **3** as against that of the methyl compound **2** could also reflect the participation of field effects, electrostatic repulsion between the bromine atom and the allyloxy group again reducing the conformational space available to the latter. The *tert*-butyl derivative **4** was expected to react much more quickly than the derivatives **2** and **3**, since the volume of free space available for the allyloxy group to move in is considerably reduced. In the event, this derivative was only marginally more reactive in producing the adduct **11**, the reaction time reducing to 7 h, with an activation energy of 71 kJ mol^{-1}. A more detailed examination of models of the available space showed that whilst the overall area occupied by the allyl group was indeed reduced, certainly secondary interactions also intervened, such that there was an unfavourable interaction between the methylene hydrogens of the allyl group and one of the methyl groups on the *tert*-butyl substituent when the azide and olefin reactants were lined up for cycloaddition (Fig. 1). This unfavourable interaction restrains formation of the transition state, *i.e.* if too large, steric buttressing can interfere with the cycloaddition process.

The azidomethyl substituent has fewer degrees of freedom than the allyloxy group and modelling studies had indicated that, for the cycloaddition reaction, the presence of an *ortho*-methyl group adjacent to the azidomethyl substituent would not enhance the rate of reaction since it is too small to inhibit completely its free rotation. This effect was demonstrated with the derivative **5**, only a slight rate enhancement being observed in cycloaddition to the oxazepine **12**, the activation energy being 94.5 kJ mol^{-1}.

This *ortho*-buttressing effect can be used to synthetic advantage. For example, the fused triazoles **13** and **14** could be prepared by cycloaddition of the corresponding prop-2-

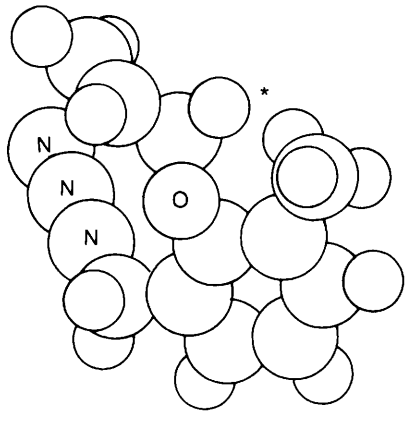


Fig. 1 Model of the proposed conformation leading to cycloaddition for **2**. For the *tert*-butyl derivative **4** a steric clash occurs in the region indicated by *.

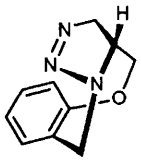


Fig. 2

ynyloxy-derivatives **6** and **7**. Whilst similar buttressing effects, were observed, the latter reacting within a few hours whereas the former took days, the bromo-buttress could be removed from compound **14**, by reduction with tributyltin hydride, to produce the parent system **13**.

A ^{1}H NMR study of the dihydrotriazole **8** showed that the five-membered ring prefers to adopt a conformation where it bends over the benzene ring (Fig. 2). The dihydrotriazoles are surprisingly heat stable, although above 150 °C they are decomposed. On treatment with dilute acids they rapidly react; with dilute acetic acid compound gave the alcohol **15**, characterised as its acetylated product **16**.

It should be noted that systems like **1** have the reacting components insulated from one another so that their cycloaddition reactions afford a simple chemical test, by means of the *ortho*-buttressing effect, for exploring the shapes and sizes of substituents. We are currently examining the spatial requirements of other cycloadditions using this matrix.

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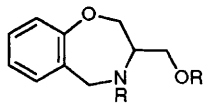

15; R = H
16; R = COMe

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