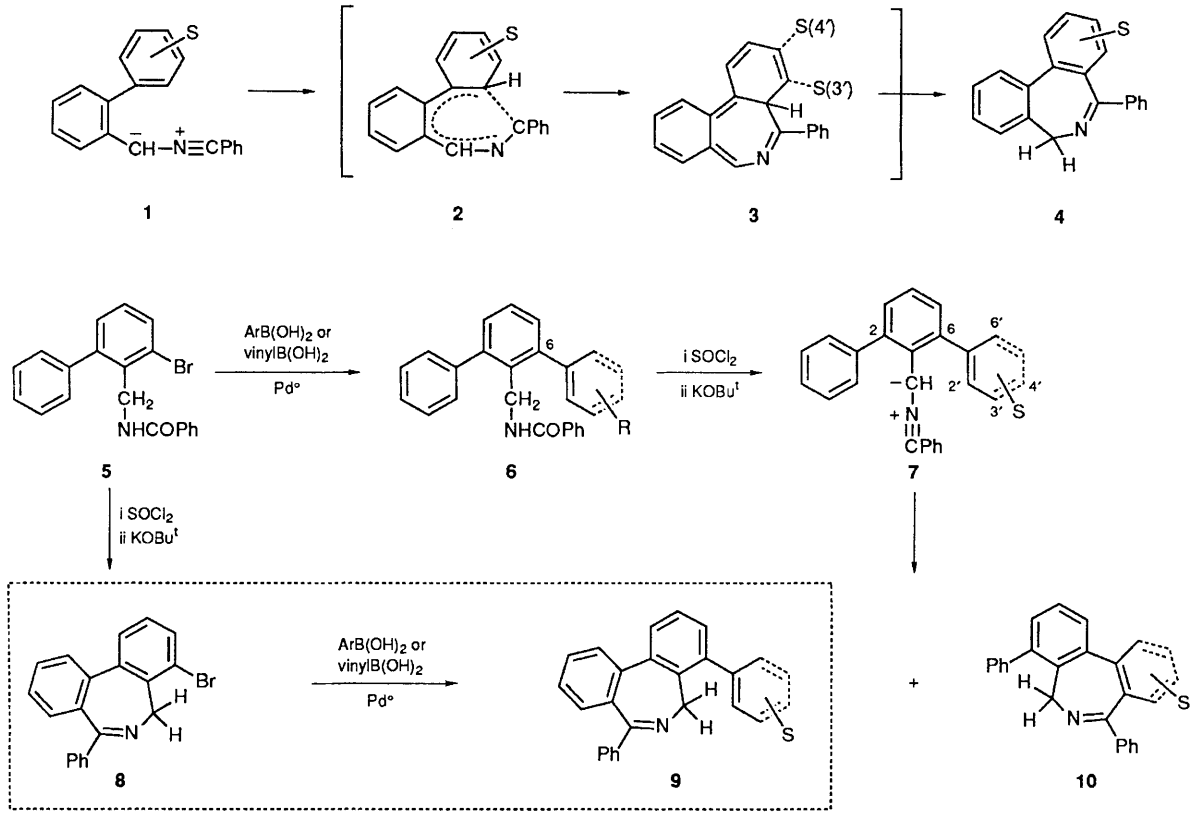
1,7-Electrocyclic Substitution by Nitrile Ylides: The Effect on the Reaction Rate of the Nature of the γ,δ-Double Bond and of Aromatic Substituents

Kevin E. Cullen and John T. Sharp*

Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, UK

In the competitive cyclisation of **7** to give **9** and **10**, all substituents in the 3′ and 4′ positions increased the overall reaction rate relative to that of the 2-phenyl ring; 6-alkenyl and -thienyl groups also reacted faster than the 2-phenyl ring.

We have recently shown that 1,7-cyclisation of nitrile ylides of the type **1**, generated from imidoyl chlorides by reaction with potassium *tert*-butoxide at 0 °C, provides a good synthetic route to the dibenz[*c*,*e*]azepine system **4**.[1] The cyclisation is effectively a substitution reaction of the terminal aromatic ring which takes place *via* two pericyclic processes; 1,7-electrocyclisation to give the intermediate **3**, followed by a [1,5]-sigmatropic hydrogen shift. In view of the synthetic potential of reactions of this type and current interest in determining and explaining the factors that control the rates of electrocyclic processes,[2] it was of interest to find out in a more quantitative sense how the cyclisation rate is affected by substituents on the aromatic ring, and by the nature of the double bond in related systems having other unsaturated groups in the γ,δ position. This has been done *via* an internal competition reaction using the system shown in Scheme 1. The nitrile ylide **7** can cyclise by the two alternative paths shown to give the azepines **9** and **10**. In all cases an unsubstituted phenyl ring in the 2-position was used as the comparator, and the nature of the 6-substituent was varied through a range including alkenyl, thienyl and a number of substituted aryl groups.



Scheme 1

The amides **6** required as precurors were prepared from **5** by the Pd^0 catalysed coupling route shown. The competitive cyclisations of **7** were carried out in THF at 0 °C and after quenching with ammonium chloride solution the crude reaction product was obtained by extraction with dichloromethane and evaporation. Chromatography was used to separate **9/10** from any other components but in most cases the isomeric products could not be separated from each other. The yields are given in Table 1. The products were identified as benzazepines by the mass spectra (low and high resolution), and the ^1H NMR (360 MHz) spectra of the mixtures. The latter showed a pair of doublets (δ 3.6–3.9 and 4.9–5.3, *J* 10.5 Hz) for each isomer which are characteristic of the C-7 methylene group of the dibenzazepine system. The NMR absorptions due to the minor isomer **9** were identified in each case by the addition to the NMR sample of a little of the 'authentic' material, prepared from **8** as shown in Scheme 1 (yields 56–99%) and fully characterised by elemental composition and mass and NMR spectra.† In cases (*a*), (*b*) and (*e*) no peaks due to isomer **9** could be detected in the mixtures under conditions in which a control experiment showed that *ca.* 1% would have been detected. In cases (*e*) and (*f*) the isomers produced by substitution at the 2′ and 6′ positions of the 3′-substituted phenyl ring were differentiated by ^1H NMR. In all cases except (*f*) the isomer ratios of the products were determined by ^1H NMR from the integrals of the C-7 methylene proton absorptions, which were well separated from other absorption peaks. In case (*f*) the integrals of the methoxy protons were used. To avoid any possible errors due to fractionation, the ratio measurements were carried out using spectra of the crude reaction products, obtained as outlined above, before any chromatography was carried out. The **10/9** ratios given in Table 1 are the average of two experiments.

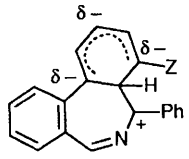
† All new compounds gave correct data from combustion analysis or high resolution mass spectrometry and had IR, NMR and mass spectra consistent with the proposed structures.

Table 1 Relative cyclisation rates for the 6-substituent in structure **7**

	Product mixture **9** and **10**	
6-Substituent	Yield(%)	Ratio **10/9**
(a) *E*-2-Phenylethenyl	97	>100[a]
(b) 2-Thienyl	97	>100[a]
(c) 3′,5′-Dimethylphenyl	96	8.3 ± 0.1
(d) 3′,5′-Bistrifluoromethylphenyl	87	32.0 ± 0.1
(e) 3′-Nitrophenyl	quant.[b]	>100[a] (2′/6′ = 2.5)
(f) 3′-Methoxyphenyl	99	6.5 ± 0.2 (2′/6′ = 7.3)
(g) 4′-Fluorophenyl	94	1.2 ± 0.1
(h) 4′-Methylphenyl	93	1.5 ± 0.1
(i) 4′-Chlorophenyl	97	2.2 ± 0.2
(j) 4′-Methoxyphenyl	96	1.6 ± 0.1
(k) 4′-Trifluoromethylphenyl	82	2.8 ± 0.1
(l) 4′-Dimethylaminophenyl	52	1.3 ± 0.2

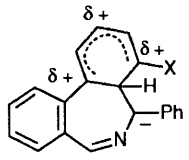
[a] Other product not detectable by NMR, detection limit <1%. [b] The 2-nitro- and 4-nitro-5,8-diphenyl-7*H*-dibenz[*c*,*e*]azepines were separated by chormatography on silica.

It is notable that in all cases the cyclisation involving the 6-substituent was faster overall than the competing cyclisation onto the unsubstituted phenyl ring. In case (*a*) reaction occurred exclusively at the alkenic double bond.[3] The nitrile ylide thus avoids the alternative reaction path, *i.e.* cyclisation on to the phenyl ring (*cf.* **1** → **3** → **4**) which would be expected to have a higher activation energy since it involves loss of the aromatic stabilisation energy of two benzene rings. Case (*b*) shows that the thiophene ring is much more reactive than phenyl. This is probably due in part to its lower aromatic stabilisation energy and the higher double bond character of the 2,3 bond, and in part to the +*R* effect of the sulphur atom as discussed below. Cases (*c*) and (*d*) show that the reactivity of aryl rings is strongly affected by 3′-substituents and that both +*I* and −*I* groups are activating. A single 3′-nitro group (−*I*,−*R*), case (*e*), had a stronger overall activating effect and,



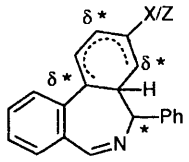
11

a; Z = CF_3
b; Z = NO_2



12

a; X = Me
b; X = OMe



13

* = +/−

in the substituted ring, directed more strongly to the adjacent 2′ position than to the alternative 6′ position. In case (*f*) the single 3′-methoxy group (−*I*,+*R*) showed moderate activation at the 2′ position. All the *para*-substituents (cases *g*–*l*) were found to be activating but to a much smaller degree.

In the interpretation of these results we make the assumption that the cyclisation step (**1** → **3**) is irreversible, as shown for a closely related reaction,[4] and that it takes place *via* a 1,7-electrocyclisation process with a helical transition state as discussed for the related diazo cyclisations[5] and confirmed by a recent *ab initio* calculation.[6] From consideration of a molecular model of the reactant **7** we conclude that the two alternative transition states for electrocyclisation are equally accessible and that the competition results are not biased by steric effects.‡ The pattern of reactivity exhibited, rate enhancement by both electron-donating and -withdrawing groups, is reminiscent of that seen in 1,3-dipolar cycloaddition reactions of Sustmann type II. It may be that the best explanation for our results will similarly involve consideration of the effects of the substituents on the energies and coefficients of the frontier orbitals of the system. However, as a first attempt at rationalisation, the effect of the substituents on the energy of the reaction intermediate **3** is discussed below in general terms of resonance and inductive effects. The assumption is then made that the transition state **2** is close enough in energy and structure to the intermediate for it to be subject to the same stabilising or destabilising effects.

‡ This applies only to the 3′- and 4′- substituents discussed here. Substituents in the 2′- position exert a strong steric effect on the course of the reaction which will be discussed elsewhere.

In cases (*c*)–(*l*) (Table 1), the aromatic substituents must *a priori* be affecting the cyclisation rate by their effect on the energies of the reactant and/or the two alternative transition states for cyclisation. The effect of the substituents on the energy of the reactant **7** is probably small since any enhanced electron delocalisation by resonance will be severely restricted by steric limitation of coplanarity between the substituted ring in the 6 position and the two adjacent groups. In contrast the transition state **2** of the electrocyclisation step has the geometry for maximum conjugation between the substituted ring and the nitrile ylide and its energy should be much affected by substituents which enhance or extend electron delocalisation. In the intermediate **3**, substituents in the 3′ position are directly conjugated through to the atoms derived from the original nitrile ylide and can, therefore, exert a strong stabilising effect *via* the contribution of dipolar canonical structures such as represented in **11** and **12**. In these structures the charge is partly localised on the 3′/5′ atoms so that X or Z substituents at these positions can exert strong stabilisation *via* either inductive or resonance effects. Dipolar contributions of this type to the transition state **2** would enhance charge separation and favour cyclisation. In contrast substituents in the 4′ position of structure **3** are not conjugated with the extended π system and are, therefore, less capable of exerting a stabilising effect. Thus, for example, in **13**, the X/Z substituent is not directly attached to the ring atoms carrying the localised charges in the dipolar canonical structure, and, therefore, the effect on the transition state energy, while still stabilising, would be expected to be much smaller. This explanation, based on the assumption that the intermediate **3** is an adequate model for the transition state **2** seems to accord with the experimental observations to date. Further work on other substituents, other unsaturated groups, and other 1,3-dipoles is in progress.

Received 23rd November 1990; Com. 0/05286H

References

1 P. W. Groundwater, C. Struthers-Semple and J. T. Sharp, *J. Chem. Soc., Chem. Commun.*, 1987, 1367.
2 D. C. Spellmeyer, K. N. Houk, N. G. Rondan, R. D. Miller, L. Franz and G. N. Fickes, *J. Am. Chem. Soc.*, 1989, **111**, 5356, and references cited therein.
3 The only product obtained was 2a,3,3a-trihydro-2a,3,7-triphenylcyclopropa[*c*]isoquinoline; see: K. R. Motion, I. R. Robertson and J. T. Sharp, *J. Chem. Soc., Chem. Commun.*, 1984, 1531. This rearranged on heating to give 3,5,9-triphenyl-(1*H*)-2-benzazepine (80%).
4 P. W. Groundwater and J. T. Sharp, *Tetrahedron Lett.*, 1987, **18**, 2069.
5 I. R. Robertson and J. T. Sharp, *Tetrahedron*, 1984, **40**, 3095.
6 K. N. Houk and J. C. Evanseck, personal communication.