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THE CYCLISATION OF BENZONITRILE 3,3-DIARYLALLYL YLIDES TO GIVE 3H-2-BENZAZEPINES: SUBSTITUENT DIRECTIVE EFFECTS AND MECHANISM

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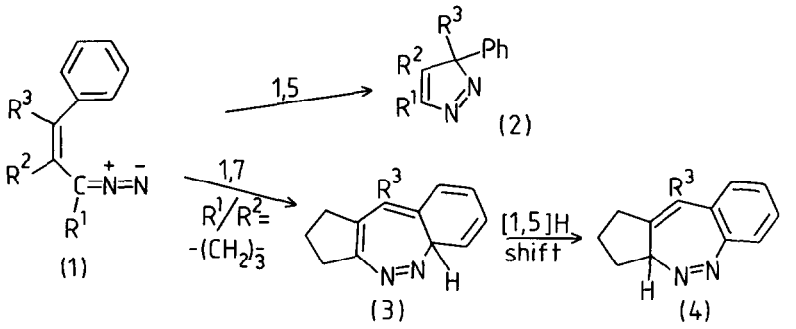
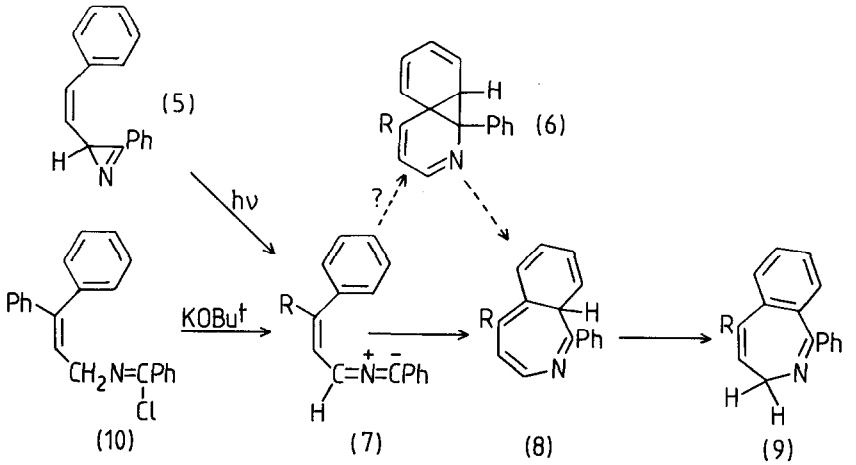
The title nitrile ylides (7), generated by the reaction of imidoyl chlorides with base, cyclised by 1,7-ring closure to give 3H-2-benzazepines (9), in contrast to analogous diazo-compounds (1) which prefer 1,5-electrocyclisation. Asymmetrically placed substituents (R in 14b) favour substitution at the ortho (2') position irrespective of their polar electronic effects. Deuterium labelling studies have shown that the cyclisation step is irreversible for nitrile ylides (14b) but reversible for diazo-compounds (14a).

This letter is concerned with a comparison between the reactions of diazo-compounds (1) with those of nitrile ylides (7) in diene-conjugated systems having α,β-olefinic and γ,δ-aromatic unsaturation. We have shown that the diazo-compounds (1) cyclise preferentially by 1,5-electrocyclisation to give 3-aryl-3H-pyrazoles (2) as the primary products.[1] However this mode of reaction can be inhibited by structural



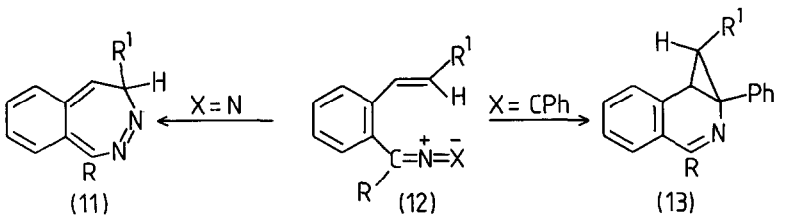
manipulation so that the alternative 1,7-closure becomes competitive, e.g. the fusion of a cyclopentyl ring at C3/C4 results in the exclusive formation of the 3H-1,2-benzodiazepine (4).[1] These results contrast with Padwa's later observations on the analogous nitrile ylide (7, R=H) which showed the opposite periselectivity and cyclised by 1,7-closure to give the 3H-2-benzazepine (9, R=H) in high yield without such structural contrivance.[2] A route via 1,7-electrocyclisation followed by a [1,5] hydrogen shift, (7) → (8) → (9), similar to that shown above for (1) → (4) was suggested.

This striking difference in periselectivity between two formally similarly intermediates, differing only in the nature of the terminal atom



of the 1,3- dipole, led to the work described here. In view of the fact that the nitrile ylide (7, R=H) had been generated by photolysis of the azirine (5) and knowing that other work had revealed differences between such reactions and those of thermally generated species, the first objective was to check the periselectivity of (7) when produced by a non-photochemical route. Utilizing a well-established general route to nitrile ylides, the imidoyl chloride (10) in THF at 0°C was treated with potassium tert-butoxide to give a deep purple colouration attributed to (7, R=Ph). After this had faded (ca 15 min) work-up gave the benzazepine (9, R=Ph), isolated in 73% yield after chromatography,[3] thus confirming that 1,7-cyclisation is the predominant reaction path of the ground state nitrile ylide. A related electrocyclic aromatic substitution reaction by a nitrile imine has recently been reported.[4]

In seeking an explanation for this periselectivity difference between (1) and (7) it seemed possible that it might result from a different mechanism of ring-closure as recently demonstrated for the analogues (12, X=N and CPh). Cyclisation of the former (and of related systems) gave



1,2-diazepines via a primary step best rationalised as a 1,7-electrocyclisation to give (11),[5] while the latter cyclised by a carbene-like 1,1-cycloaddition to give (13).[6] A similar first step for (7) would involve the formation of (6) as an intermediate, subsequently ring-opening to give (8). In an effort to detect a major difference in mechanism of this sort we have investigated the directive effects of asymmetrically placed substituents in the aromatic ring of the nitrile ylide (14b) to compare with a similar study on the diazo cyclisation (14a)

published earlier.[7] The cyclisation of a range of substituted nitrile ylides (14b, R=Me, MeO, Cl, CF_3) was carried out using the method above to give mixtures of ((16b) - produced by cyclisation ortho to the substituent - and (18b) via cyclisation para to the substituent. The ratios were measured by ^1H n.m.r. spectroscopy on the crude products before chromatography.[8] The results are given in Table 1 together with those for the comparable diazo cyclisation of (14a).[7] The o/p ratios for R=Me, MeO, and Cl show a strong similarity between the two dipoles but that for CF_3

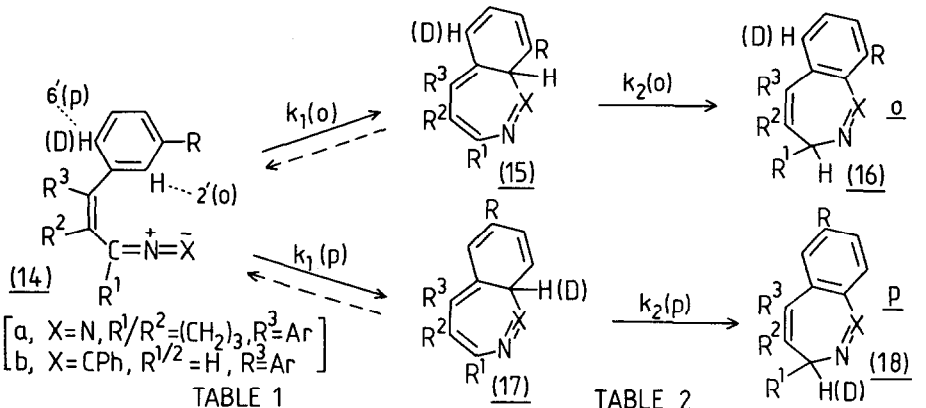


TABLE 1

directive effect	o/p ratio			
substituent R	Me	MeO	Cl	CF_3
DIAZO [X=N]	3·6	1·8	2·7	0·64
N.Y. [X=CPh]	2·5	1·5	2·1	1·5

TABLE 2

effect of D on o/p ratio for R=Me				
no D	6'-D	2'-D	k_1	k_2
3·6	13·4	0·99	⇄	→
2·5	2·1	2·4	→	→

differs. In the diazo case the deuterium isotope effect was used to show that the cyclisation steps (k_1(o) and k_1(p)) are reversible under the cyclisation conditions. Thus, for (14a, R=Me), substitution of D for H at the 6' position as illustrated (D), resulted in a strong diversion of the course of the reaction from para to ortho attack (see Table 2) and vice versa for D substitution at the 2' position. In contrast similar deuterium substitution in the nitrile ylide cyclisation of (14b, R=Me) resulted in no appreciable change in the o/p ratio (Table 2) showing that in this case the cyclisation steps leading to (15b) and (17b) (possibly via intermediates of type (6)) are irreversible - a clear difference between the two 1,3-dipoles.

In the nitrile ylide reaction this result shows that the substituents must be exerting their directive influence - whatever form this takes - on the cyclisation step and not on the subsequent hydrogen shift. The preference for ortho attack irrespective of the polar electronic influence of the substituent is interesting, unexpected and not at present understood, but it is clearly inconsistent with a transition state stabilised by either electron donation or electron withdrawal adjacent to the site of substitution. Thus it is not easy to reconcile these directive effects with a carbenic 1,1-cycloaddition giving (6) as the first

step - assuming typical electrophilic character of the carbene centre. There is not much comparable data in the literature on substituent directive effects in carbene cyclisation but recent results by Shechter on intermolecular carbenic aromatic substitution have shown that MeO and Cl clearly exert different and opposite directive effects with MeO favouring carbene addition to either the 1,2 or 2,3 bond whereas Cl favours addition to the 3,4 bond.[9] This contrasts with the putative (7) → (6) type reaction which would require 2,3 addition to be more strongly favoured by Cl than by MeO.

If as therefore seems likely both the diazo and nitrile ylide reactions proceed via 1,7-electrocyclisation then the difference in 1,5/1,7 periselectivity must be due to a difference in some property of the two 1,3-dipoles which affects the relative activation energies of the two modes of cyclisation. The ease of in-plane bending is probably important since the transition state for 1,5-electrocyclisation must require more bending of the dipole than that for 1,7-electrocyclisation. In-plane bending disrupts and weakens the orthogonal π-bond beween the N and the terminal atom of the dipole (N-X in (14) and it might be expected that bending of the diazo group, involving disruption of the relatively weak N=N, would be easier than bending the nitrile ylide with its stronger N=C. This accords with the observed results.

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Notes and References

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3. m.p. 137-138°C (picrate m.p. 173-175°C) correct analysis on both; ^{1}H n.m.r. CH_2 δ 3.10 (dd, J 10.3 and 6.7 Hz), 4.48 (dd, J 10.3 and 7.3 Hz), T_c 350 K.

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8. The cyclisation yields were generally very high as shown by n.mr. spectra of the crude products but losses occurred on chromatography on both silica and alumina. Small samples of each isomer were separated by preparative t.l.c. and identified by accurate mass measurement and high resolution ^{1}H and ^{13}C n.m.r. The ratios given are a mean of duplicate experiments consistent to ±8% or better.

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