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SUBSTITUENT DIRECTIVE EFFECTS IN 1,2-BENZODIAZEPINE SYNTHESIS VIA ELECTROCYCLIC AROMATIC SUBSTITUTION BY THE DIAZO-GROUP: A REARRANGEMENT OF 9- TO 7-SUBSTITUTED 3H-1,2-BENZODIAZEPINES

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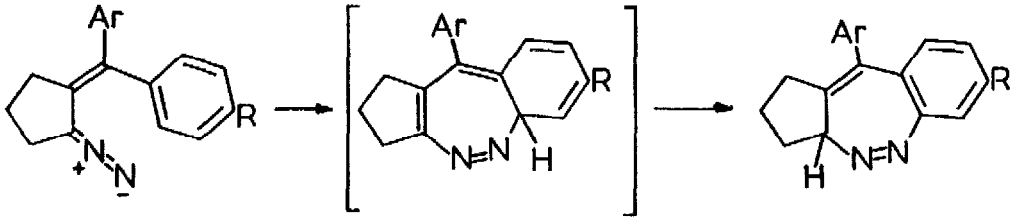
Abstract: The directive effect of aryl-substituents on the site of ring closure in the electrocyclisation of 1-aryl-3-diazoalkenes has been investigated. At 80°C the product ratio is determined by kinetic control but for some substituents the kinetically favoured 9-substituted 3H-1,2-benzodiazepines undergo a new rearrangement to their more stable 7-substituted isomers.

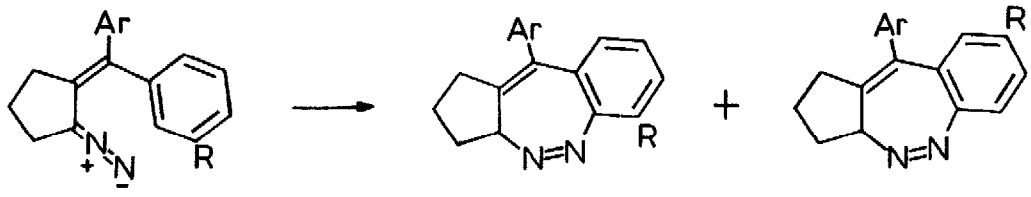
We recently reported the synthesis of 1,2-benzodiazepines (3) from the unsaturated diazo-compounds (1) via an 8π electron electrocyclic ring closure and subsequent [1,5] sigmatropic hydrogen shift.[1]



(1) (2) (3)

This letter is a preliminary report on the reactions of the meta substituted diazo-compounds (4) which can in principle cyclise to give either or both of the isomeric diazepines (5) and (6) via substitution at positions ortho or para to the group R.

The results for a variety of substituents (R) are shown in the Table; both isomers were obtained in all cases except where R=Bu^t (4 g) which gave only the less hindered product (6 g). The isomeric diazepines were separated by chromatography (1000 x 15 mm, silica) and the isomer ratios were determined by h.p.l.c. using the isolated diazepines for calibration.



(4) (5) (6)

R = Me, Et, OMe, OEt, Cl, Bu^t, CF_3 (see table)

[Ar = m-C_6H_4R]

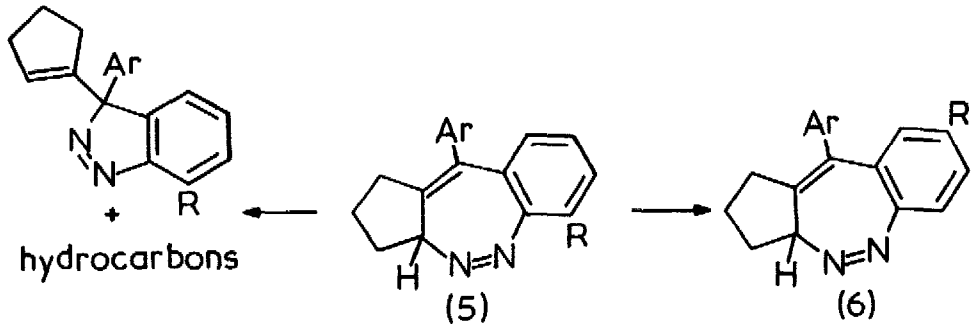
TABLE

Diazo-compound[+]	Total isolated yield of benzodiazepines (%)	Isomer ratio (5)/(6)
(a) Me	74	4.3
(b) Et	74	3.5
(c) OMe	70	1.6
(d) OEt	75	1.6
(e) Cl	78	1.9
(f) CF_3	62	0.5
(g) Bu^t	64	(6) only

[+] Reaction carried out in dry cyclohexane under reflux.

It can be seen from the Table that alkyl- (apart from Bu^t), alkoxy-, and chloro-groups favour ortho attack with methyl having the strongest directive effect, while trifluoromethyl favours para. The preference for ortho substitution in (4a-e) would seem to result from kinetic control of the product ratio since the favoured products (5) would be expected to be sterically destabilised with respect to the para isomers (6). Examination of Dreiding models of (5a-e) shows crowding in all cases as the substituent R is closer to the azo nitrogen than the sum of their van der Waals radii. This predicted difference in thermodynamic stability between (5) and (6) was readily demonstrable in some cases. Thus the isolated ortho isomers (5c,d,e) rearranged to the para isomers (6c,d,e) when heated at 80-110°C in dry hydrocarbon solvents. The conversions were relatively slow [ca 14% in 17 h for (5c) and (5d) and only 2% in 17 h for (5e)] at 80°C so the product ratios recorded in the Table after 1 h reaction time approximate closely to the true kinetically controlled ratios. For these alkoxy- and chloro-substituted diazepines the rate of rearrangement of (5) to (6) was very much faster than the

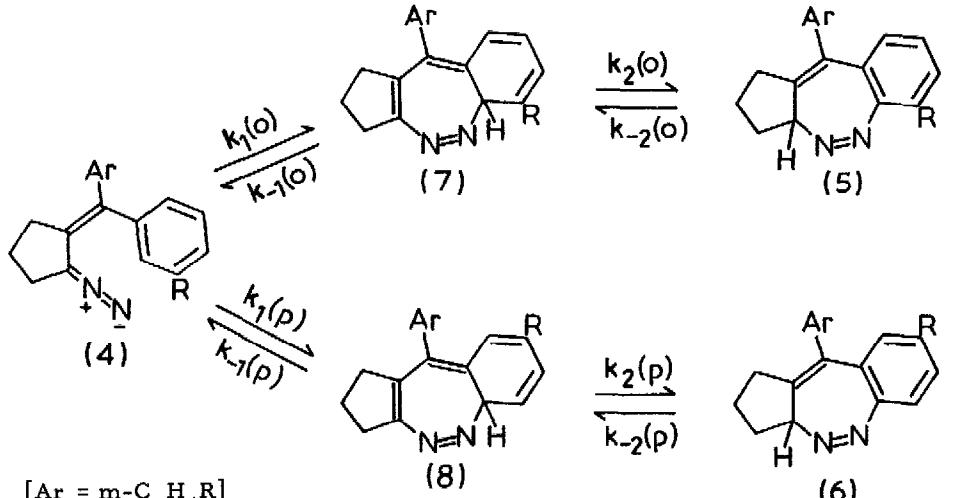
alternative previously reported thermal reaction path leading to indazoles, Scheme 1, and hydrocarbon products.[3]



[Ar = m-C_6H_4R]

Scheme 1

In contrast however the alkyl diazepines (5a, b) were stable at 80°C e. g. (5a) showed no measurable conversion to (6a) and very little thermal decomposition after 17 h. At higher temperatures some (5a) to (6a) conversion did take place but only in a minor reaction path compared to indazole and hydrocarbon formation. This reluctance of the alkyl diazepines to undergo the ortho to para isomerisation reaction seems likely to be due to kinetic rather than thermodynamic factors since (5a, b) would be expected to be more sterically destabilised by the bulky alkyl groups than (5c, d, e) by the alkoxy- and chloro-groups (E_s = +0. 99, +0. 18, and 0 for OMe, Cl, and Me respectively).[4] A control reaction showed that the reverse reaction (6a, b) → (5a, b) did not take place.



[Ar = m-C_6H_4R]

Scheme 2

In connection with the two competing isomerisation reactions of the diazepine shown in Scheme 1, it is worthy of note that the transformation to the indazole is also photo-induced but the conversion to the isomeric diazepine is not, thus the ortho isomers (5) can be readily converted to indazoles by exposure to daylight at room temperature without competition from para diazepine formation.

In the cyclisation reaction the origin of the directing effects of the substituents is not yet understood. The diazepines are formed in a two-step process (Scheme 2), so the directive influence of the substituents could be exerted in either or both steps. The limited conclusions which can be drawn at present are: (i) at 80°C k_{-1} and/or k_{-2} must be very slow or zero (depending on the nature of R) so that the product ratio is essentially under kinetic control, and (ii) alkoxy- and chloro-groups lower the activation energy for one or both of the reverse steps [k_{-1} (o), k_{-2} (o)] so that at higher temperatures or on prolonged heating at 80°C the kinetically favoured isomers rearrange to the more stable products via (5) → (7) → (4) → (8) → (6).

Mechanistic studies on this reaction are in progress and will be reported in the full paper. We thank the Science Research Council for support (H. R. S. and T. K. M.).

REFERENCES

1. J. T. Sharp, R. H. Findlay, and P. B. Thorogood, J. C. S. Perkin I, 1975, 102.
2. C. D. Anderson, J. T. Sharp, and R. S. Strathdee, J. C. S. Perkin I, 1979, 2730.
3. J. N. Done, J. H. Knox, R. McEwan, and J. T. Sharp, J. C. S. Chem. Comm., 1974, 532.
4. R. W. Taft, "Steric Effects in Organic Chemistry" ed. M. S. Newman, Wiley, New York, 1956, Chap. 13.

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