Steric Effects in the Cyclisation of Diazoalkenes: a New Route to 1,2-Benzodiazepines

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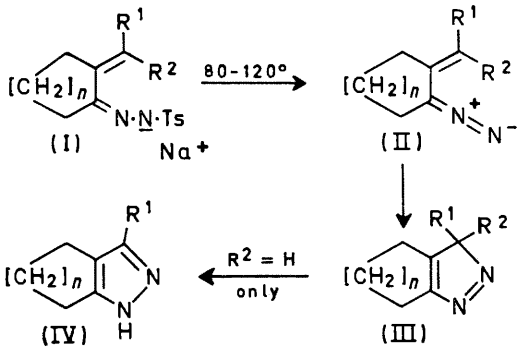
Summary The sodium salts of the tosylhydrazones of α-dialkylmethylenecyclopentanones do not cyclise to give 3*H*-pyrazoles but decompose *via* loss of nitrogen to give dienes, whereas their diarylmethylene analogues cyclise to give 1,2-benzodiazepines in good yield.

THE cyclisation of the alkali-metal salts of αβ-unsaturated tosylhydrazones to give 1*H*- and 3*H*-pyrazoles has been reported by other workers;[1-3] for example, the tosylhydrazone of 2-isopropylidenecycloheptanone [Scheme 1; (Ia)] gave the 3*H*-pyrazole (IIIa) in 68% yield.[3] We now report a remarkable discontinuity of behaviour in the reactivity of compounds of this type.

The methylenecyclohexanone derivatives (Scheme 1; $n = 2$) react 'normally' and cyclise to give pyrazoles† in good yield *e.g.* (IIIb) (87%), (IIIc)(73%), and (IVd) (77%). However, the cyclopentanone analogues ($n = 1$) cyclise to pyrazoles *only* when $R^2 = H$, *e.g.* to give the aromatic 1*H*-pyrazoles (IVe) (71%) and (IVf) (82%). In all these cases the course of the reaction is little affected by the

† All new compounds gave satisfactory elemental analyses.

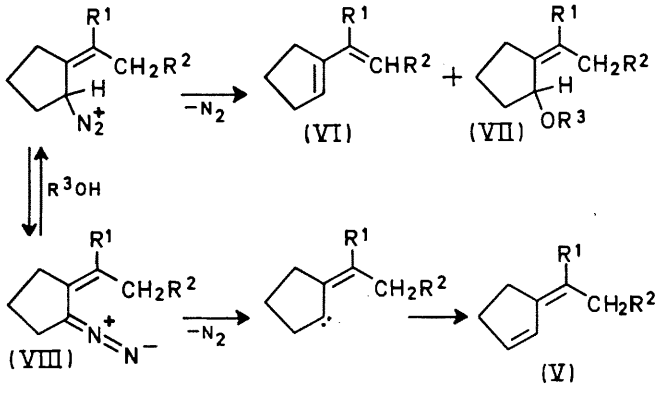
protonicity[4] of the solvent, showing that cyclisation of the diazoalkene intermediate is fast compared with competing protonation by the solvent.



(a) $n = 3$; $R^1 = R^2 = Me$ (d) $n = 2$; $R^1 = Ph$, $R^2 = H$
(b) $n = 2$; $R^1, R^2 = -[CH_2]_5-$ (e) $n = 1$; $R^1 = Ph$, $R^2 = H$
(c) $n = 2$; $R^1 = R^2 = Ph$ (f) $n = 1$; $R^1 = Me$, $R^2 = H$
Ts = tosyl

SCHEME 1

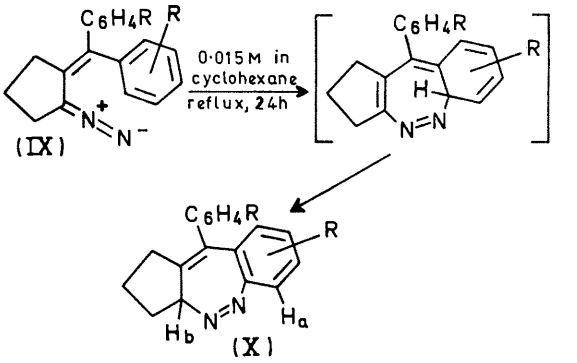
However, when $n = 1$ and both R^1 and R^2 are alkyl groups (Scheme 2) the diazoalkene intermediate reacts only *via* loss of nitrogen to give (V) (a, 70%; b, 74%) in aprotic solvents, and (VIa) (32%), (VIIa) (31%) in ethylene glycol monomethyl ether.



(a) $R^1,R^2 = -[CH_2]_3-$ and (b) $R^1 = Me$, $R^2 = H$;
$R^3 = MeOCH_2CH_2-$

SCHEME 2

Brewbaker and Hart[5] recently concluded that diazoalkene cyclisation to 1*H*-pyrazoles involves an intramolecular 1,3-dipolar cycloaddition. An electrocyclic reaction of this type could well be sensitive to steric factors; and the clear-cut difference in the reactivity of (IIb and c) and (VIII a and b) may be due both to the greater distance between the ends of the π-system in the latter, and to the greater blocking effect of the alkyl group in the more rigid methylenecyclopentane system, which combine to prevent (VIII) attaining the transition state required for cyclisation. At the moment we have insufficient evidence to distinguish between this and the alternative explanation that (V) and/or (VI) and (VII) are formed *via* the intermediacy of an unstable 3*H*-pyrazole *e.g.* (III; $n = 1$, $R^1 = R^2 = Me$).



SCHEME 3

When $n = 1$ and R^1 and R^2 are aryl groups the decomposition of the diazoalkene (II) takes yet another course—a novel cyclisation on to the *o*-position of the aromatic ring (Scheme 3) providing a route to otherwise inaccessible[6] 1,2-benzodiazepines. The structures of the diazepines were deduced from their reductive cleavage and by spectroscopic methods; *e.g.* (X; R = H) gave a mass spectrum with a small parent peak *m/e* 260 and major peaks at 232, 205, and 191; its n.m.r. spectrum showed 9 aromatic to 7 aliphatic protons; a doublet at τ 2·15 was assigned to H_a (this became a bs at τ 2·42 when R = *p*-Me‡) and a multiplet at τ 6·85 was assigned to H_b. When R = Me or OMe the two alkyl groups showed different chemical shifts. The reaction gives good yields for a variety of substituents (R = H, 80%; *p*-Me, 68%; *p*-CF_3, 56%; *m*-OMe, 68%). In an experiment carried out in the presence of tributylphosphine, the characteristic red of the diazoalkene (IX; R = H) was not observed and no diazepine was obtained; instead the diazoalkene was intercepted by a fast reaction with the phosphine to give a phosphazine which hydrolysed during the work-up to give 2-diphenylmethylenecyclopentanone hydrazone (85%). This result indicates that diazepine formation involves the cyclisation of the diazoalkene intermediate (IX) and not direct cyclisation of its tosylhydrazone sodium salt precursor. The experimental evidence is consistent with the mechanism shown in Scheme 3, *i.e.* an electrocyclic ring-closure followed by a [1,5]-sigmatropic hydrogen migration.

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‡ Refers to position of substituent in (IX).

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