Tetrahedron Letters No. 45, pp 4337 - 4342, 1971. Pergamon Press. Printed in Great Britain.

STERIC COURSE AND REGIOSELECTIVITY IN THE CYCLOADDITIONS OF DIAZOACETIC ESTER TO TRANS- AND CIS-CINNAMIC ESTER

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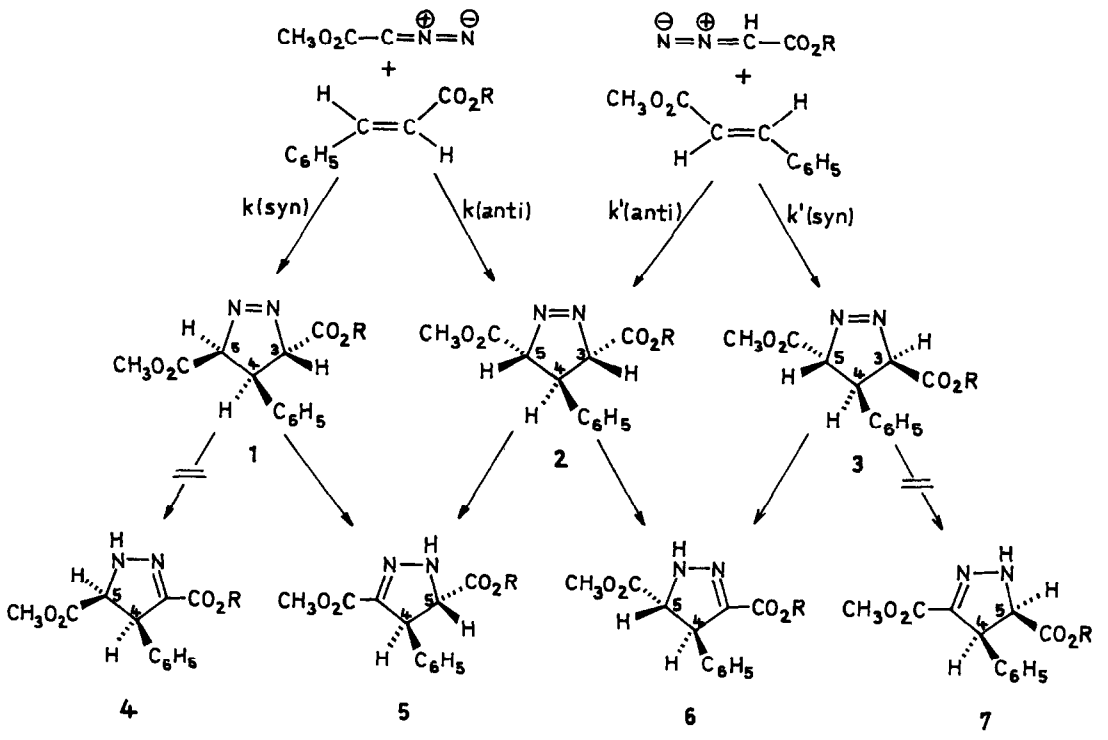
(Received in UK 6 September 1971; accepted for publication 8 October 1971)

Buchner (1) discovered the cycloaddition of diazoalkanes to carbon-carbon double bonds to form 1-pyrazolines. The latter compounds tautomerise to 2-pyrazolines if the double bond can become conjugated with for e.g. an ester group, but even in such systems 1-pyrazolines have been shown to be the primary adducts (2,3).

In 1893 Buchner and Dessauer (4) reported that methyl diazoacetate + ethyl trans-cinnamate and ethyl diazoacetate + methyl trans-cinnamate combined to give isomeric 2-pyrazolines, both of which produced the same methyl ethyl 4-phenylpyrazole-3,5-dicarboxylate on dehydrogenation (5). The formation of isomers was surprising and has remained unexplained for the last 78 years. Brey and Jones (6) assigned structures 5a and 6a to the two isomers on the basis of their n.m.r. spectra.

In our hands, methyl diazoacetate reacted with ethyl trans-cinnamate in 325 hr at 52° to give 90% of an adduct mixture, which contained 73% 5a, 17% 6a and 10% of a 5-phenyl-2-pyrazoline derivative (see below). The product ratio was independent of reaction time. Analysis of the OCH_3 singlets in the n.m.r. spectra showed that the ratio 5a : 6a was 80 : 20, averaged over several experiments. Ethyl diazoacetate and methyl trans-cinnamate produced 93% of an adduct mixture in 367 hr at 52°. The major products 5a and 6a were present in a 20 : 80 ratio, and here also were accompanied by 9% of a 5-phenyl-2-pyrazoline.

The 2-pyrazolines 5a and 6a are expected to be formed via the three diastereomeric 1-pyrazolines 1a - 3a. In the tautomerisation step, the 3-H or 5-H is transferred to the nitrogen atom, and we assume that deprotonation takes place from the less hindered side, i.e. trans to 4-C_6H_5 if possible. This assumption is justified by the absence of the cis-disubstituted 2-pyrazolines



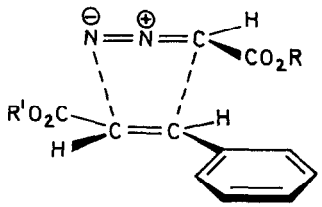
4a and 7a among the products.

Evidence for the steric and electronic similarity of CO_2CH_3 and $CO_2C_2H_5$ comes from the finding that 5a and 6a were formed in the ratios 80 : 20 and 20 : 80, respectively, in our two cycloaddition systems. These inverse ratios are expected if the two ester groups exert similar influences in adduct formation, if the tautomerisations 1a → 5a and 3a → 6a take place at the same rate and if protons 3-H and 5-H are involved to an equal extent in the tautomerisation of 2a.

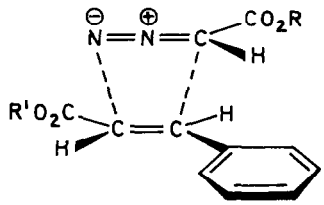
The configuration of the olefinic dipolarophile is always retained in the products of 1,3-dipolar cycloadditions (7). In the scheme k(syn) and k(anti) designate the rate constants of the two concerted cycloadditions that take place via the "two-planes" orientation complexes (7,8) 8 and 9. The relation

$$\frac{k(syn)}{k(anti)} = \frac{[\underline{\underline{1a}}]}{[\underline{\underline{2a}}]} = \frac{[\underline{\underline{5a}}] - [\underline{\underline{6a}}]}{2[\underline{\underline{6a}}]} = \frac{k'(syn)}{k'(anti)}$$

allows the calculation of k(syn) / k(anti) = 1.5. This result shows that the syn-transition state is slightly favoured over the anti arrangement. The π-overlap of ester group and phenyl in the syn-complex $\underline{\underline{8}}$, and in its corresponding transition state, presumably overcomes the adverse van der Waals repulsion of these substituents. Both effects are probably negligible in the anti-complex $\underline{\underline{9}}$.



8 *syn*



9 *anti*

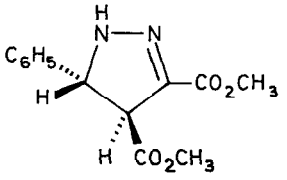
By an increase in the size of the ester alkyl, the van der Waals repulsion should become the dominant effect. The cycloaddition of tert.-butyl diazoacetate to methyl trans-cinnamate reached 90% yield after 258 hrs. at 52° and produced $\underline{\underline{5b}}$ and $\underline{\underline{6b}}$ in the ratio 34 : 66. The structural assignments rest on dehydrogenation by bromine and on the n.m.r. spectra; the OCH_3 singlets allowed quantitative analysis (9). The calculated k'(syn) / k'(anti) is 0.47 and verifies the prediction that the anti-transition state should be the favoured one.

Analogously, the reaction of methyl diazoacetate and tert.-butyl cinnamate furnished after 324 hr at 52° 96% of an adduct mixture which contained $\underline{\underline{5b}}$ and $\underline{\underline{6b}}$ in a 86 : 14 ratio corresponding to k(syn) / k(anti) = 2.57.

In the "normal" orientation of cycloaddition the diazoalkane carbon becomes bonded to the β-position of the α,β-unsaturated ester. Therefore, the afore-mentioned 5-phenyl-2-pyrazolines are products of an "anomalous" orientation. After treating methyl diazoacetate and methyl trans-cinnamate for 212 hr at 50°, we isolated 10% of the 5-phenyl-2-pyrazoline $\underline{\underline{10}}$ in addition to 84% of the "normal" product $\underline{\underline{16}}$, which has been reported earlier (4). The reaction of methyl diazoacetate to methyl cis-cinnamate (960 hr, 52°, 86%) provided even

a higher percentage of the anomalous adduct 11 : the product contained 11, 16 and 17 in the ratio 29 : 43 : 28. Structure proof for 10 and 11 was obtained by conversion to 3-phenylpyrazole, and through synthesis (in a 85 : 15 ratio) by addition of phenyldiazomethane to dimethyl maleate.

The configurations of 10 and 11 follow from the principle of retention of dipolarophile structure in the concerted cycloaddition and are confirmed by the AB spectra of the ring protons : 10, τ 6.03, 4.77, $J_{4,5}$ = 9.6 Hz; 11 τ 5.74, 4.68, $J_{4,5}$ = 13.2 Hz.



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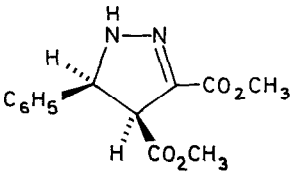
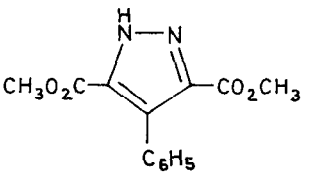


11

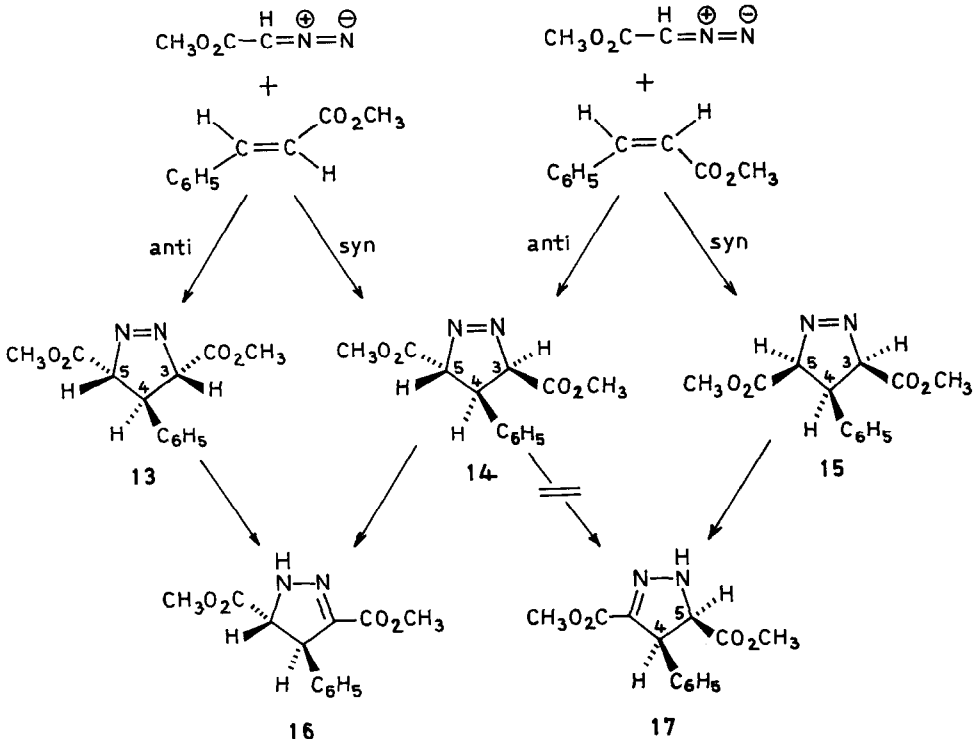


12

"Anomalous" directions of diazoalkane cycloadditions to acetylenic esters (10), α,β-unsaturated nitro compounds (11) and sulfones (12, 13) have been occasionally observed.

The 4-phenylpyrazolines 16 and 17 which are the "normal" adducts from methyl trans- and cis-cinnamate, furnished the same pyrazole 12 on dehydrogenation, and 12 in turn was converted to 4-phenylpyrazole. The trans- and cis-configuration of 16 and 17 follow from their progenitors and are supported by the n.m.r. spectra (16: $J_{4,5}$ = 4.1 Hz, 17: $J_{4,5}$ = 12.4 Hz).

By application of the same principles that were discussed above to the additions to methyl trans- and cis-cinnamate, the 1-pyrazolines 13 and 14 should be the precursors of 16, whereas 17 should arise from 15 only. The ratio of the steric courses, k(syn) / k(anti), is expected to be 1.5 for methyl diazoacetate + methyl trans-cinnamate as was found earlier for the methyl ethyl ester combinations. In contrast, the ratio drops to 0.64 for the addition to methyl cis-cinnamate. Possible reasons are discussed in the following communication.



We gratefully acknowledge the financial assistance given by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

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