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α-DIAZOCARBONYL COMPOUNDS AND ENAMINES - A DICHOTOMY OF REACTION PATHS

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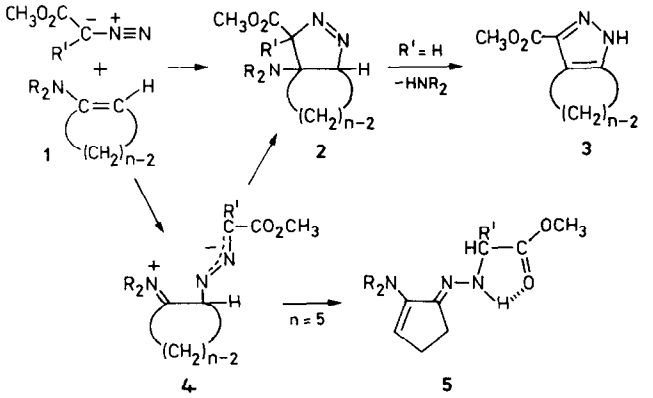
Summary 2,5-Dimethyl-1-pyrrolidinocyclopentene produces with methyl diazoacetate and diazoketones 2-pyrazolines as cycloadducts whereas with dimethyl diazomalonate an azo coupling equilibrium is established. The rate constants of these two reactions respond differently to solvent polarity.

N-Cyclohexenyldialkylamines 1, n = 6, and enamines derived from open-chain carbonyl compounds undergo 1,3-dipolar cycloadditions with diazoacetic ester [1,2] or diazomalonic ester [2] to give 1-pyrazolines 2 which subsequently may tautomerize to 2-pyrazolines and eliminate HNR_2 to yield pyrazoles 3.[1,2] 1-Diethylaminopropyne follows the same pattern and furnishes with the two α-diazocarboxylic esters a pyrazole and a 3H-pyrazole, respectively.[3] In contrast, N-cyclopentenyldialkylamines 1, n = 5, experience azo coupling and the resulting zwitterion 4 tautomerizes to the conjugated enamine-hydrazone 5.[4] The crystalline zwitterion 4, n = 5, R_2N = pyrrolidino, R' = CO_2CH_3, was isolated and shown to entertain an equilibrium with 5 in solution.

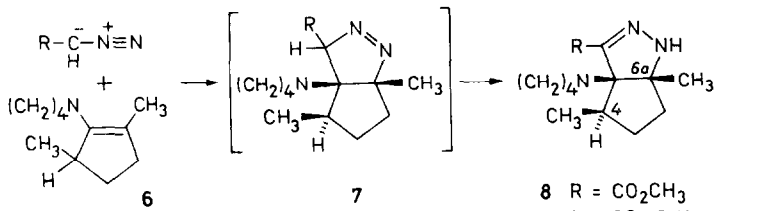


One would expect a preference for azo coupling with increasing charge stabilization of the zwitterion 4. However, even the highly nucleophilic 1-pyrrolidinocyclohexene combines with dimethyl diazomalonate to give the 4-amino-2-pyrazoline 14 through a cycloadduct 2. On the other hand, we isolated 51 % 5, R_2N = morpholino, R' = H, and only 1 - 2 % 3, n = 5, from the reaction of 1-morpholinocyclopentene and methyl diazoacetate; morpholine is a weaker base than pyrrolidine and in 4, R' = H, the negative charge is less stabilized than in 4, R' = CO_2CH_3. Attempts of interconverting enamine-hydrazones and cycloadducts failed. Which factors determine the reaction course ?

A. Experiments with 2,5-Dimethyl-1-pyrrolidinocyclopentene

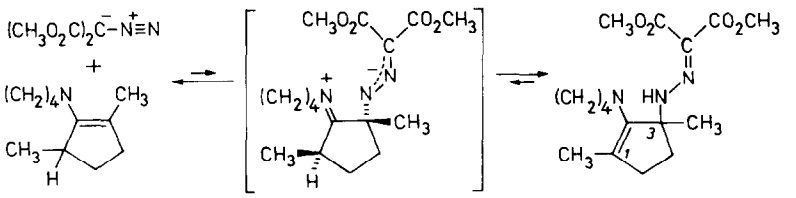
Model 6 was chosen, because the methyl groups will block the aromatization of the cycloadduct,

2 → 3, as well as the two-fold prototropy, 4 → 5, subsequent to azo coupling.



6 7 8 R = CO_2CH_3 9 R = $CO-C_6H_5$ 10 R = $CO-C_6H_4-NO_2\,p$

The reactions of 6 with methyl diazoacetate, diazoacetophenone and its p-nitro derivate (3 d, 25°C) provided the 2-pyrazolines 8 (72 %, mp 116-118°C), 9 (95 %, mp 130-131°C) and 10 (94 %, mp 132-134°C).[5] There was no evidence for the occurence of stereoisomers; the approach of the diazo compound from the less hindered side may be assumed. NMR of 8 ($CDCl_3$): τ 3.4 (s, br, NH), 6.21 (s, OCH_3), 8.58 (s, 6a-CH_3), 8.86 (d, J = 7.0 Hz, 4-CH_3).



6 11 12

The pale yellow crystals of 12 precipitated from the ether solution of 6 and dimethyl diazomalonate in ether at -30°C (81 %, mp 51-53°C); IR (KBr): 1513 (C=N), 1663 cm^{-1} (enamine C=C); NMR ($CDCl_3$): τ -1.9 (s, br, NH), 6.03 and 6.15 (2 s, 2 OCH_3), 8.23 (s, 3-CH_3), 8.51 (s, 1-CH_3). Thus, the initial azo coupling product 11 was converted to 12 by proton shift. The enamine group in 12 was established by hydrolysis with moist silicagel at -20°C to give an oxohydrazone in syn,anti isomers; cycloaddition of p-nitrophenyl azide to the enamine double bond took place at -30°C.

The solution of 12 in $CHCl_3$ shows the IR absorption for diazomalonic ester (2140, 1759 cm^{-1}), revealing a mobile equilibrium with the reactants. The NMR spectrum allowed a quantitative determination of the equilibrium (NH for 12, ester signals at τ 6.03, 6.13, 6.15 for 12 + diazomalonate) and indicated a strong temperature dependence:

In Chloroform at °C	-49	-29	-8	+8	+32	+55
% 12	99	87	81	68	45	26
In Chlorobenzene °C	+8	+32	+55	+84	+126	
% 12	80	65	43	20	1	

The reversibility of the spectral changes on heating and cooling disclosed the virtual absence of side reactions. From the association constants at various temperatures the thermodynamic parameters for 12 formation were evaluated:

In Chloroform $\Delta H = -8.4 \pm 1.5$ kcal mol^{-1}, $\Delta S = -26 \pm 4$ e.u.

Chlorobenzene $\Delta H = -10.8 \pm 1.5$ kcal mol^{-1}, $\Delta S = -32 \pm 4$ e.u.

The mobility of the equilibrium which produces 12 is noteworthy. It was conceivable that the fast equilibration would be slowly disturbed by an irreversible 1,3-dipolar cycloaddition which should give a 1-pyrazoline. However, after 16 h refluxing of 12 in pure chloroform under argon the NMR spectrum revealed only the equilibrium partners and no cycloadduct. Supposedly, thermodynamic effects thwart the cycloaddition. Whereas the 1-pyrazoline 7 from 6 + diazoacetic ester tautomerizes to the 2-pyrazoline 8, the quaternary carbon atom in a 1-pyrazoline from 6 + diazomalonic ester would prohibit the stabilization of the cyclic azo function to the hydrazone group.

How are the cycloadducts 8-10 formed? Two mechanistic pathways must be considered for the precursor, the 1-pyrazoline of type 2, as illustrated above: the one-step concerted cycloaddition and the two-step sequence via the zwitterion 4. The dependence of the rate constant on solvent polarity belongs to the few mechanistic criteria which can be applied here.

B. Solvent Dependence of the Competing Reactions

The solvent-dependent equilibrium 6 + dimethyl diazomalonate causes complications. Therefore, we measured the kinetics of two other reactions of diazomalonic ester, the azo coupling with 1-pyrrolidino-cyclopentene affording 4, n = 5, $R_2N = (CH_2)_4N$, $R' = CO_2CH_3$, which in solution equilibrates with 5,[4] and the cycloaddition to 1-pyrrolidinocyclohexene providing the 2-pyrazoline 14. The concentration of dimethyl diazomalonate was monitored by the extinction of the IR diazo absorption at or near 2129 cm^{-1}.

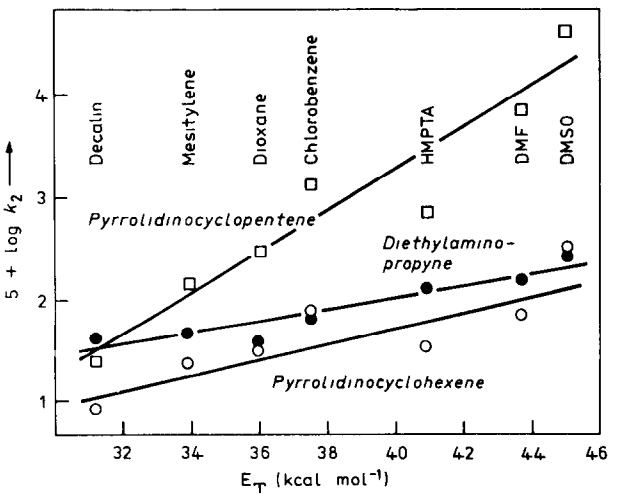
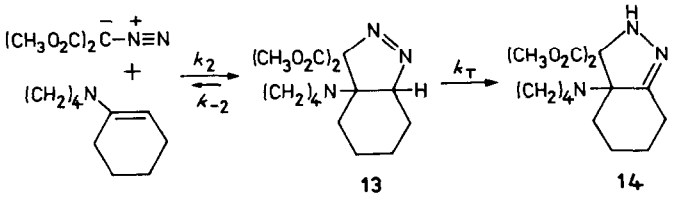


Figure 1. Plot of log k_2 for reactions of dimethyl diazomalonate vs. E_T

Table I. Dipole Moments (Debye) in Benzene at 25°C

Dimethyl diazomalonate	2.55
1-Pyrrolidinocyclopentene	1.59
1-Pyrrolidinocyclohexene	1.52
1-Diethylaminopropyne	1.17



13 14

The rate constants were determined at 80.3°C in seven solvents (Fig. 1) and reveal a higher solvent influence on the azo coupling than on the cycloaddition; the empirical parameter E_T [6] served as a measure of solvent polarity. k_2(Dimethyl sulfoxide) / k_2(Decalin) amounted to 1 540 for 1-pyrrolidinocyclopentene and to 41 for 1-pyrrolidinocyclohexene.

The 2+2 cycloadditions of tetracyanoethylene to enol ethers via a zwitterionic intermediate [7] show an even higher solvent dependence than the generation of the zwitterion 4 by azo coupling with pyrrolidinocyclopentene. The reactants have higher dipole moments here (Table I) and, therefore, one expects a smaller increase of charge separation on the way to the zwitterion.

Although small, the solvent influence for dimethyl diazomalonate + pyrrolidinocyclohexene is still on the higher side compared with other 1,3-dipolar cycloadditions. [8] We included data for 1-diethylaminopropyne + diazomalonate - the product is 4-diethylamino-5-methyl-3H-pyrazole-3,3-dicarboxylic ester [3] - in Fig. 1; also here the polarity influence is positive with k_2(DMSO) / k_2(Decalin) = 6.3. We ascribe the low solvent dependence of the reactions of pyrrolidinocyclohexene and diethylaminopropyne to the concerted nature of the cycloaddition, but caution is appropriate in the first example, because a conceivable solvent influence on the partition coefficient of 14 formation, $k_T / (k_{-2} + k_T)$, has not been ruled out.

Why does pyrrolidinocyclohexene not undergo azo coupling with diazomalonic ester ? It probably does as judged from the red color after mixing and the rapid disappearance of up to 10 % diazomalonate. It appears likely that an azo coupling equilibrium is established and that 14 is the result of a slow competing cycloaddition. The negligible difference in the dipole moments of pyrrolidinocyclopentene and -cyclohexene (Table I) cannot be responsible for the divergence of reactivity. There must be an unidentified influence of the ring size.

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