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ELECTROPHILIC REACTIONS OF DMAD WITH A CYCLIC DIENAMINE: SOLVENT INFLUENCE UPON THE COMPETITIVE FORMATION OF [4+2]-,[2+2]- AND MICHAEL TYPE ADDUCTS

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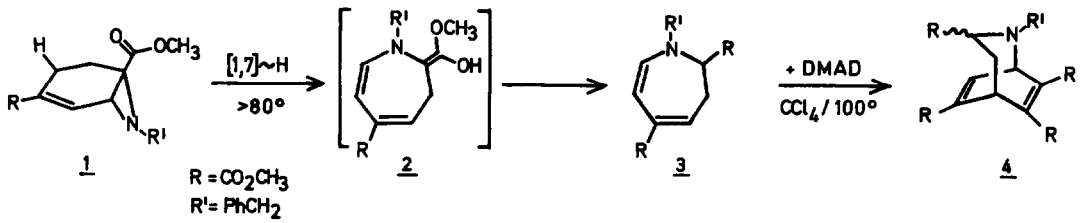
Summary. The reaction course of DMAD with dihydroazepine 3 depends strongly on the solvent: under appropriate conditions either 4, 5 or 6(E) is formed as the exclusive addition product.

In a recent communication we reported on the formation of the Diels-Alder adduct 4, utilised as one structural proof for the dihydroazepine 3 which can be generated from 1 through a thermal [1,7]-H-homotrienyl shift [1]. Even though the straightforward [4+2]-cycloaddition of 3 with dimethyl acetylenedicarboxylate (DMAD) is consistent with the high reactivity of electron rich dienes towards electron deficient olefins [2], it was intriguing that 4 was the only reaction product and that no indication of the enamine character of 3 (i.e. the ability to react in a [2+2]-manner) [3] has been obtained.

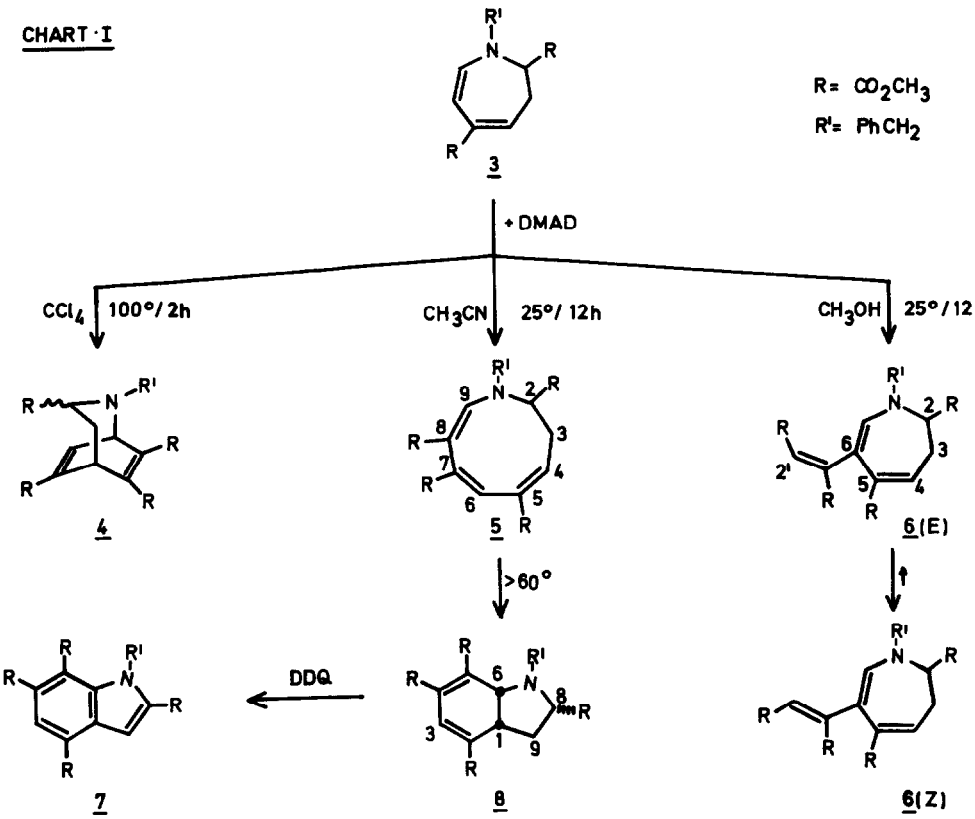


1 2 3 4

During a more thorough investigation, however, the appearance of 4 as the sole addition product turned out to be purely accidental and due to the fact that carbon tetrachloride had been chosen as the solvent. Here we describe the remarkably strong influence of various solvents upon the course of the reaction with DMAD, which allows a qualitative correlation between solvent polarity (E_T-values) and product distribution to be drawn.

Depending on the reaction medium, formation of one of three isomeric 1:1-cycloadducts can be induced in a completely selective way: For instance, while the bicyclic diene 4 is produced in carbon tetrachloride at about 100°C, reaction in acetonitrile as well as in methanol takes place even at room temperature leading to a single product in each case, namely the azacyclononatriene 5 and the 6-vinyl-2,3-dihydroazepine 6(E), respectively, the yields of isolated products being 80-90% (see Chart I).

CHART·I



The structure of the monocyclic triene 5 is assigned on the basis of the spectroscopic data (vide infra) and the observation, that on heating a clean transformation into the tetrahydroindene 8 takes place ($t_{1/2}$ (75°C, C_6D_6) = 80 min); oxidation of 8 with DDQ leads to the indene 7. The cis-fusion of the five- and six-membered rings in 8 (substantiated by the coupling constant $J_{1,6}$ = 11.8 Hz) [4] corroborates the proposed all-cis configuration of 5 [5] assuming, as is reasonable, that the 6e-cyclisation 5 ⟶ 8 is a disrotatory process. At elevated temperatures the third reaction product, 6(E), undergoes geometrical isomerisation around the exocyclic C=C-bond leading to 6(Z) in a reversible step (at 75°C in $CDCl_3$ equilibrium is reached after ca. 8h with (Z)/(E) in the ratio 6:1) [7].

If the addition of DMAD is carried out in benzene, bromobenzene, nitrobenzene or DME at 114°C, mixtures of 4 and 8 are obtained with equally good over-all yields (see Table); no 6 could be detected in these cases.

For an interpretation of the experimental results two basic reactions of dihydroazepine 3 with DMAD have to be considered (see Chart II): (1) Diels-Alder type cycloaddition affording 4 [8] and (2) formation of the dipolar species 10, which either reacts under ring closure to give 9 (followed by rapid ring opening to the observed monocycle 5) or, in the presence of protic solvents, leads after protonation and deprotonation to the Michael adduct 6(E) [9].

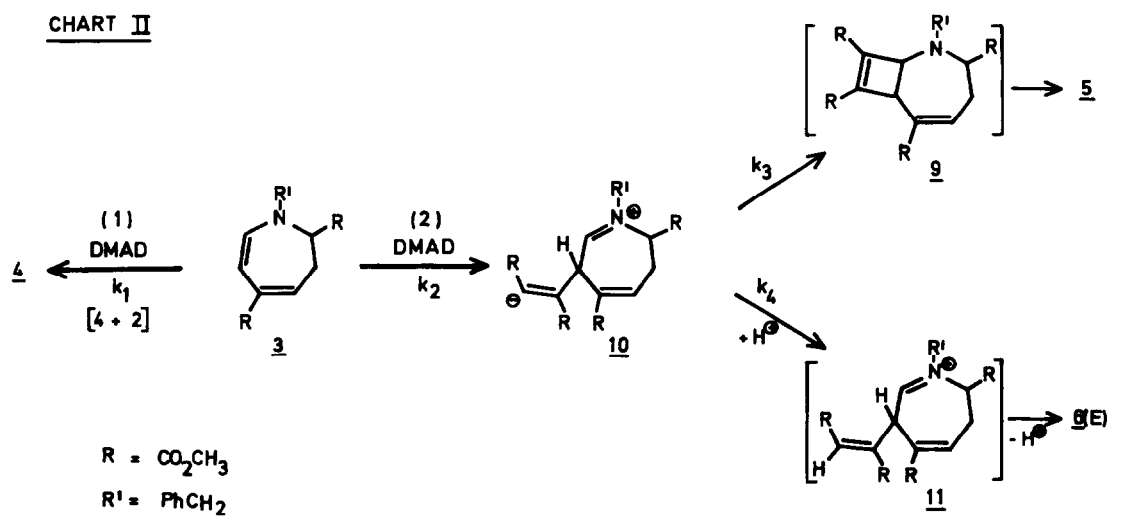
Table. Half Lives and Product Distribution for the Reaction of 3 with DMAD in Different Solvents at 114°C [a]

solvent	E_T-values[10] [kcal/mol]	$t_{1/2}$[b] [min]	products[c] 4	5 and/or 8	6
CCl_4	32.5	ca. 200	100	-	-
C_6H_6	34.5	ca. 190	70	30	-
C_6H_5Br	37.5	ca. 120	60	40	-
DME	38.2	ca. 80	50	50	-
$C_6H_5NO_2$	42.0	ca. 60	35	65	-
CH_3CN	46.0	ca. 3	-	100	-
CH_3OH	55.5	ca. 3	-	-	100

a) Molar ratio of 3 and DMAD. Higher concentrations of DMAD considerably affect both the reaction time and product distribution: Whereas the reaction in CCl_4 with a 2-3 fold excess of DMAD at 100°C gave 4 as the sole adduct within 2h (Chart I), the use of a 10-20 fold excess afforded a mixture of 4 and 5/8 requiring an even shorter time for complete conversion.- b) Determined by ^{1}H-NMR spectroscopy.- c) Relative yields in percent.

This mechanism is in excellent agreement with the following observations (see Table and Chart II) [11]: (i) Use of the least polar solvent in this series gives rise to formation of 4 as the only product ($k_1 \gg k_2$). (ii) With increasing polarity of the (aprotic) medium the relative portion of 4 decreases in favor of 5 (for CH_3CN: $k_1 \ll k_2$). (iii) There exists a qualitative correlation between solvent polarity and the reaction yields of 4 (relatively apolar transition state) and 5 (polar transition state); limiting E_T-values for the exclusive formation of 4 or 5 (6) are 32 and 46, respectively. (iv) In protic solvents like methanol the Michael adduct 6(E) is the only product ($k_4 \gg k_3$). (v) The relative rates for the formation of 5 and 6 do not depend on the solvent; the rate limiting step for both pathways is the generation of dipole 10 ($k_2 \ll k_3$, k_4).

CHART II



5 : mp 123°C (CCl_4); UV (CH_3CN): $\lambda_{max}(\varepsilon)$= 274 nm (13370); ^{1}H-NMR (360 MHz, $CDCl_3$): τ= 2.6-2.8 (Ph-H), 2.34 (9-H), 2.7 (6-H), 3.71 (4-H), 4.75 (2-H), 5.63/5.88 ($N-CH_2$), 6.20/6.28/6.31/6.36 (OCH_3), 7.3-7.4 (3-H); $J_{2,3a}$/$J_{2,3b}$= 7.0/11.5, $J_{3a,4}$/$J_{3b,4}$= 4.5/7.5, J_{N-CH_2}= 14.5 Hz.

6(E): UV (CH_3CN): $\lambda_{max}(\varepsilon)$= 335 nm (9050); ^{1}H-NMR (360 MHz,$CDCl_3$): τ= ~2.65(m-, p-Ph-H), 2.75(o-Ph-H), 3.33 (4-H), 3.36 (7-H), 3.40 (2'-H), 5.51/5.60 ($N-CH_2$), 5.62(2-H), 6.24/6.28/6.36/6.48 (OCH_3), 6.92/7.65 (3-H); $J_{2,3a}$= 5.5, $J_{2,3b}$=2, $J_{3a,3b}$= 14.5, $J_{3a,4}$=8.8, $J_{3b,4}$= 5.5, J_{N-CH_2}= 15.0 Hz.

6(Z): ^{1}H-NMR (360 MHz,$CDCl_3$; data taken from the spectrum of the 6:1- mixture with 6(E)):τ=~2.64(m-,p-Ph-H), 2.78(o-Ph-H), 3.11(7-H), 3.34(4-H), 4.66 (2'-H), 5.54($N-CH_2$), 5.65(2-H), 6.15/6.30/6.35/6.36 (OCH_3), 6.99/7.67 (3-H); $J_{2,3a}$= 5.5, $J_{2,3b}$= 2.0, $J_{3a,3b}$=14.0, $J_{3a,4}$=8.5, $J_{3b,4}$= 6.2 Hz.

7 : mp 117°C (MeOH); UV (CH_3CN): $\lambda_{max}(\varepsilon)$= 355 (8500,sh), 342 (10200,sh), 315 (15700), 256 (27900,sh), 248 nm (30200); ^{1}H-NMR (90 MHz,$CDCl_3$): τ= 1.44/1.88 (3-H/5-H), 2.7-2.8 (m-,p-Ph-H), 3.2 (o-Ph-H), 4.06 ($N-CH_2$), 5.96/6.10/6.15/6.51 (OCH_3).

8 : mp 115°C (MeOH); UV (CH_3CN): $\lambda_{max}(\varepsilon)$= 296 nm (4650); ^{1}H-NMR (360 MHz, $CDCl_3$): τ= 2.69 (3-H), 2.7-2.8 (Ph-H), 5.41 (6-H), 5.96/6.04 ($N-CH_2$), 6.18/6.21/6.22/6.39 (OCH_3), 6.33 (1-H), 6.54 (8-H), 7.61/8.01 (9-H); $J_{1,3}$= 1, $J_{1,6}$= 11.8, $J_{1,9a}$=7.0, $J_{1,9b}$= 12.0, $J_{8,9a}$= 1, $J_{8,9b}$= 7.5, $J_{9a,9b}$= 12.0, J_{N-CH_2}= 13.5 Hz.

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2) R.Sustmann, Pure Appl.Chem.40, 569 (1974).
3) Review: D.N.Reinhoudt, Adv.Heterocycl.Chem. 21, 253 (1977).
4) W.Eberbach, Chem.Ber. 107, 3287 (1974), and references therein.
5) Additional evidence for this geometry comes from a detailed ^{13}C-NMR analysis 6).
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7) Interestingly, the reaction of 6(E) with N-phenyltriazolinedione takes place exclusively at C-7 and C-2', while 6(Z) gives rise to the corresponding endocyclic Diels-Alder product (attack at C-4 and C-7) 6).
8) Reactions of this type have been reported for other 2,3-dihydroazepines: L.A.Paquette, J.Am.Chem.Soc. 86, 4092 (1964); S.R.Tanny, F.W.Fowler, ibid. 95, 7320 (1973).
9) Analogous behavior of a dipole similar to 10 (formed by the reaction of DMAD with Fischer's base) has previously been observed by Fleury et al.: C.Hubschwerlen, J.P.Fleury, H.Fritz, Tetrahedron 32, 3031 (1976).
10) C.Reichardt, Solvent Effects in Organic Chemistry, Verlag Chemie, 1979.
11) For a theoretical treatment of the competition between [4+2]- and [2+2]-cycloaddition reactions and pertinent solvent effects see N.D.Epiotis, J.Am.Chem.Soc. 94, 1924 (1972).

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