160. Reactions of 3-(Prop-2-enylidene)azetidin-2-ones with 4,5-Dihydro-3*H*-1,2,4-triazole-3,5-diones

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Dedicated to Prof. *Gunther Seitz*, Marburg, on the occasion of his 60th birthday

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The 3-(2-propenylidene)-β-lactams **1a–c** react as semicyclic dienes with the dihydrotriazole-diones **2** in a stereoselective fashion leading to the cycloadducts **3**. The 3′,3′-disubstituted derivative **4** gives no [4 + 2]-cycloaddition products but forms the adducts **5** and **6**. Stereochemistry and reaction pathways are discussed.

Introduction. – In a previous paper, we have described the synthesis of the 3-(2-propenylidene)-β-lactams **1** and their reactions with tetracyanoethylene (TCNE) and maleinimides [1]. We showed that the reactivity of the semicyclic diene system in **1** strongly depends on the configuration, especially on the possibility of forming the s-*cis*-conformation. In addition and continuation, we here describe some *Diels-Alder* reactions of **1** with the much more reactive [2] dihydro-triazole-diones **2**.

Results. – The propenylidene β-lactams **1** include two diene systems, the fixed hetero diene represented by the C=O group and the C=C bond at C(3), and the flexible all-C system at C(3). As the reactivity of **2** is much higher than that of tetracyanoethylene (TCNE) or maleinimides, one has to consider both systems as targets of the cycloadduct formation. All reaction were carried out in THF at −78°. At higher temperature or in other solvents, either no reaction products were obtained, or decomposition rapidly occurred, and, therefore, the yield of isolated product was drastically lowered. Compounds (*E*)-**1a** and (*Z*)-**1a** show clean and fast reactions with **2a** or **2b** to **3a** and **3b**, respectively, thus demonstrating that both isomers easily can reach the same s-*cis*-conformation of the diene system, and that this system is favored in the cycloaddition compared to the hetero-diene (*Scheme 1*). Azetidinones **1b** and **1c**, with a Me or Ph substituent at C(3′), exhibit some differences in their behavior. While the (*Z*,*E*)-isomers[2]) of **1b** and **1c** react as fast as **1a**, the (*E*,*E*)-isomer of **1b** either reacts only at higher temperature (−20°), or the time needed to complete the reaction has to be extended from 30 to 120 min. Under identical conditions, (*E*,*E*)-**1c** gave no adducts with **2a** or **2b**. It has to be highlighted that the (*E*,*E*)- and (*Z*,*E*)-isomers of **1a** and **1b** give identical adducts **3** in all experiments. This is clearly demonstrated by the NMR spectroscopic data of the crude reaction mixtures and supported by following the reaction course by TLC.

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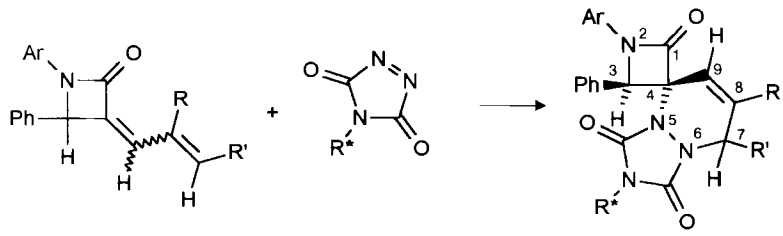
[2]) The first symbol marks the configuration of the C(3)=C(1′) bond.

Scheme 1



1a R=Me, R'=H
b R=H, R'=Me
c R=H, R'=Ph

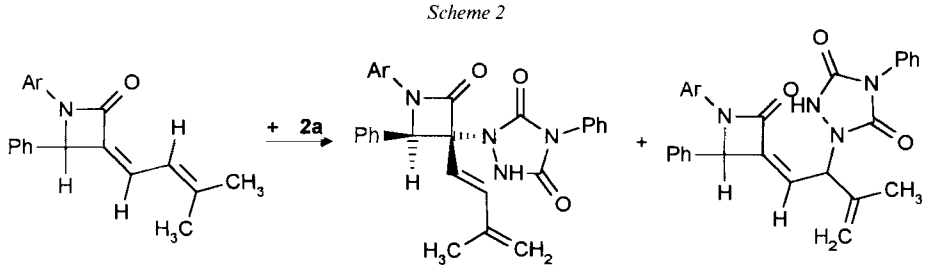
2a R*=Ph
b R*=Me

3a R=Me, R'=H, R*=Ph
b R=R*=Me, R'=H
c R=H, R'=Me, R*=Ph
d R=H, R'=R*=Me
e R=H, R'=R*=Ph
f R=H, R'=Ph, R*=Me

Ar=4-MeO–C_6H_4

In accordance with our previous results [1], the 3′,3′-dimethyl-substituted compound **4** gave no cycloadduct of structure **3**, neither at higher temperature nor in the presence of *Lewis* acids like (dichloro)(ethyl)aluminium. When the reaction between **4** and **2a** was carried out in refluxing THF, we obtained no product from a reaction with the hetero-diene but a mixture of two products, **5** and **6**, which were separated by fractional crystallization from MeOH (*Scheme 2*).

Scheme 2



4 **5** **6**

Ar=4-MeO–C_6H_4

The ^{1}H-NMR spectra of all compounds **3** exhibit an identical pattern. The signal of the MeO group is found at 3.73–3.75 ppm, the proton at C(3) gives a *s* between 5.7 and 6.1 ppm, and the system H–C(7), H–C(8), H–C(9) usually is represented by 3 *dd* showing vicinal and allylic coupling constants depending on the structure and position of the substituents (see *Exper. Part*). In the ^{1}H-NMR spectra of **3c** and **3d**, H–C(7) is represented by a *m* with coupling constants of 5 Hz (Me), 4.5 Hz (H–C(8)), and 1.5 Hz (H–C(9)). The spectra of **3e** and **3f** show analogue coupling constants for the coupling between H–C(7), and H–C(8) and H–C(9). It seems to be not possible to deduce the relative configuration at C(7) from these values, as both possible configurations should give similar coupling constants for the protons of the allylic system. All IR spectra are mainly characterized by 3 strong C=O bands, the highest (1775 cm^{-1}) and the lowest (1705 cm^{-1}) are caused by the dihydrotriazole-dione part, the band around 1750 cm^{-1} stands for the β-lactam moiety.

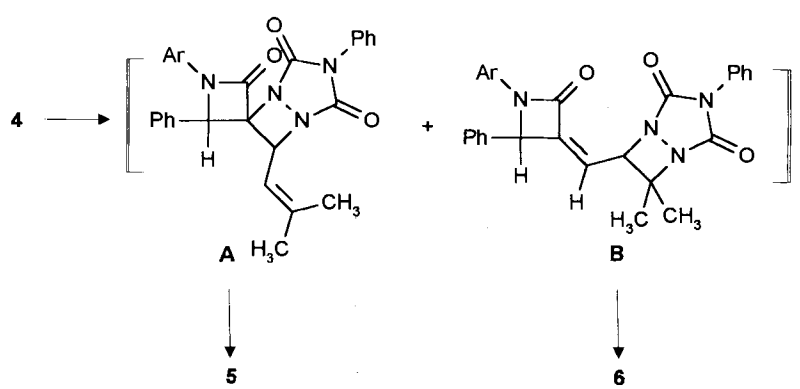
The IR spectra of **5** and **6** also show bands of C=O groups, and in addition, a strong NH signal. Furthermore, a band at 1655 cm^{-1} in the spectrum of **5** and at 1652 cm^{-1} in that of **6** may be correlated with the methylidene structure (1,1-disubstituted C=C bond). The final structure of **5** is elucidated by an homonuclear correlated

2D-NMR spectrum. The structure of **6** is in full agreement with the spectroscopic data, from which, in the ^{1}H-NMR spectrum, the signal of the proton at C(2′) (substituted by the dihydrotriazole-dione) at 4.79 ppm, the signal of H–C(1′) at 6.22 ppm, the signal of H–C(4) at 5.32 ppm, and the two signals at 4.61 and 4.67 ppm of the protons of the $=CH_2$ group are the most characteristic.

Discussion. – In all our experiments, the carbon system is much more favored for an addition than the hetero-diene system. In solution, (*E*,*E*)- and (*Z*,*E*)-isomers of **1** are in equilibrium between s-*cis*- and s-*trans*-conformation. Assuming that the attack of the dienophil prefers the less hindered side of the molecule (s-*cis*), *i.e.*, from the opposite direction to the bulky Ph group at C(4), it seems to be reasonable to expect products with the configuration (3*R**,4*R**) (*trans*) in the lactam part. The propenylidene-β-lactams may be compared with substituted buta-1,3-dienes [3] [4]. Their reactivity in *Diels-Alder* reactions is controlled not only by the energy level of the frontier orbitals but also sterically by the complexity and position of the substituents. Furthermore, MMX calculations [5] of **1b** and **1c** indicate, that the (*Z*,*E*)-isomers are the better dienophils, and that the s-*trans*-conformation of (*E*,*E*)-**1c** is stabilized as a planar system by conjugation between the lactam, the diene system, and the Ph group. Considering this, reactivity and even the steric course of the reactions of **1a–c** are understandable. Isomerization of (*E*,*E*) to (*Z*,*E*) seems to be included in the reactions of **1b**, and (*E*,*E*)-**1c** did not react under our conditions.

On the other hand, the β-lactam derivative **4** behaves like an 1,1,4,4-tetrasubstituted buta-1,3-diene, from which is known that, due to steric interaction, the formation of the s-*cis*-conformation is nearly impossible. It behaves like a 'frozen' s-*trans*-conformer [4], and, therefore, does not allow any *Diels-Alder* reaction. The formation of **5** and **6** at higher temperature might be explained by a reaction pathway *via* **A** and **B**, respectively (*Scheme 3*). Adduct **6** is formally the product of an ene reaction [6]. As described in [7] [8] for the reaction of 2,5-dimethylhexa-2,4-diene with **2a**, a diazetidine intermediate might be formed by [2 + 2] addition. In contrast to the symmetrical literature example, **4** contains an unsymmetrical diene system allowing the formation of two different [2 + 2] adducts.

Scheme 3



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Experimental Part

General. THF was dried with $CaCl_2$ and distilled over $LiAlH_4$ prior to use. Other solvents were dried according to standard procedures. M.p.: not corrected: *Linström* apparatus. CC with silica gel (*Merck* No. 7734). IR Spectra (cm^{-1}): *Perkin-Elmer IR 841, IR 1310, Beckman IT 4240*; in KBr [9]. NMR Spectra: *Bruker WP80, Varian Unity 300, Bruker WM400* for ^1H; δ in ppm rel. to Me_4Si as internal standard, J in Hz; values from 80-MHz spectra in $CDCl_3$, if not noted otherwise [9]. Elementary analyses were performed at the Pharmazeutisches Institut or Chemisches Laboratorium der Universität Freiburg i.Br.

General Procedure. At −78°, **1** is added with stirring to a soln. of an equimolar amount or maximal 10% excess of **2** in an appropriate amount of THF. When the reaction is complete (TLC), MeOH is added, and the solvents are evaporated *in vacuo*. The residue is recrystallized as noted below.

*2-(4-Methoxyphenyl)-8-methyl-1-oxo-3,*N*-diphenyl-2,5,6-triazaspiro[3.5]non-8-ene-5,6-dicarboximide* (**3a**). *a*) From (*E*)-**1a** (350 mg, 1.15 mmol) and **2a** (201 mg, 1.15 mmol): 280 mg (49%) of **3a**. *b*) From (*Z*)-**1a** (350 mg, 1.15 mmol) and **2a** (201 mg, 1.15 mmol): 349 mg (61%) of **3a**. Colorless crystals. M.p. 225–225.5° (MeOH). IR: 1765, 1760, 1705 (CO). ^{1}H-NMR: 1.70 (*s*, Me); 3.73 (*s*, MeO); 4.04 (br. *s*, 2 H–C(7)); 5.25 (*m*, H–C(9)); 5.78 (*s*, H–C(3)). Anal. calc. for $C_{28}H_{24}N_4O_4$ (480.53): C 69.99, H 5.03, N 11.66; found: C 70.07, H 5.13, N 11.58.

*2-(4-Methoxyphenyl)-8,*N*-dimethyl-1-oxo-3-phenyl-2,5,6-triazaspiro[3.5]non-8-ene-5,6-dicarboximide* (**3b**). From (*E*/*Z*)-**1a** (500 mg, 1.64 mmol) and **2b** (185 mg, 1.64 mmol): 310 mg (46%) of **3b**. Colorless platelets. M.p. 133° (MeOH). IR: 1775, 1755, 1705 (CO). ^{1}H-NMR: 1.66 (*s*, Me); 3.13 (*s*, MeN); 3.74 (*s*, MeO); 3.93 (br. *s*, 2 H–C(7)); 5.18 (*m*, H–C(9)); 5.70 (*s*, H–C(3)). Anal. calc. for $C_{23}H_{22}N_4O_4$ (418.46): C 66.02, H 5.30, N 13.39; found: C 66.13, H 5.34, N 13.29.

*2-(4-Methoxyphenyl)-7-methyl-1-oxo-3,*N*-diphenyl-2,5,6-triazaspiro[3.5]non-8-ene-5,6-dicarboximide* (**3c**). From (*Z*,*E*)-**1b** (510 mg, 1.7 mmol) and **2a** (298 mg, 1.7 mmol): 623 mg (76%) of **3c**. Colorless crystals. M.p. 227° (MeOH). IR: 1775, 1750, 1710 (CO). ^{1}H-NMR (400 MHz): 1.39 (*d*, J = 5, Me); 3.74 (*s*, MeO); 4.61 (*m*, J = 5, 4.5, −1.5, H–C(7)); 5.43 (*dd*, J = 10.5, −1.5, H–C(9)); 5.92 (*dd*, J = 10.5, 4.5, H–C(8)); 6.05 (*s*, H–C(3)). Anal. calc. for $C_{28}H_{24}N_4O_4$ (480.53): C 69.99, H 5.03, N 11.66; found: C 70.04, H 4.97, N 11.52.

*2-(4-Methoxyphenyl)-7,*N*-dimethyl-1-oxo-3-phenyl-2,5,6-triazaspiro[3.5]non-8-ene-5,6-dicarboximide* (**3d**). From (*E*,*E*)/(*Z*,*E*)-**1b** (410 mg, 1.3 mmol) and **2b** (147 mg, 1.3 mmol): 429 mg (79%) of **3d**. Colorless crystals. M.p. 148° (MeOH). IR: 1770, 1750, 1705 (CO). ^{1}H-NMR: 1.34 (*d*, J = 5, Me); 3.11 (*s*, MeN); 3.75 (*s*, MeO); 4.51 (*m*, H–C(7)); 5.39 (*dd*, J = 10.5, −1.5, H–C(9)); 5.86 (*dd*, J = 10.5, 4.5, H–C(8)); 5.95 (*s*, H–C(3)). Anal. calc. for $C_{23}H_{22}N_4O_4$ (418.46): C 66.02, H 5.30, N 13.39; found: C 66.29, H 5.18, N 13.52.

*2-(4-Methoxyphenyl)-1-oxo-3,7,*N*-triphenyl-2,5,6-triazaspiro[3.5]non-8-ene-5,6-dicarboximide* (**3e**). From (*Z*,*E*)-**1c** (500 mg, 1.35 mmol) and **2a** (237 mg, 1.35 mmol): 472 mg (72%) of **3e**. Colorless crystals. M.p. 227.5° (MeOH). IR: 1770, 1755, 1710 (CO). ^{1}H-NMR (400 MHz): 3.74 (*s*, MeO); 5.63 (*dd*, J = 4.5, −1.5, H–C(7)); 5.75 (*dd*, J = 10.5, −1.5, H–C(9)); 6.03 (*dd*, J = 10.5, 4.5, H–C(8)); 6.14 (*s*, H–C(3)). Anal. calc. for $C_{33}H_{26}N_4O_4$ (542.60): C 73.05, H 4.83, N 10.33; found: C 73.25, H 4.86, N 10.41.

*2-(4-Methoxyphenyl)-*N*-methyl-1-oxo-3,7-diphenyl-2,5,6-triazaspiro[3.5]non-8-ene-5,6-dicarboximide* (**3f**). From (*Z*,*E*)-**1c** (500 mg, 1.35 mmol) and **2b** (153 mg, 1.35 mmol): 610 mg (94%) of **3f**. Colorless crystals. M.p. 199° (MeOH). IR: 1775, 1755, 1705 (CO). ^{1}H-NMR: 2.98 (*s*, MeN); 3.73 (*s*, MeO); 5.50 (*dd*, J = 5, 2, H–C(7)); 5.61 (*dd*, J = 11, 2, H–C(9)); 5.95 (*dd*, J = 11, 5, H–C(8)); 6.09 (*s*, H–C(3)). Anal. calc. for $C_{28}H_{24}N_4O_4$ (480.53): C 69.99, H 5.03, N 11.66; found: C 69.87, H 5.08, N 11.65.

Reaction of (E/Z)-**4** *with* **2a**. Under N_2, **2a** (587 mg, 3.3 mmol) dissolved in a few ml of THF is added drop by drop to a refluxing soln. of (*E*/*Z*)-**4** (1.0 g, 3.12 mmol) in THF (20–30 ml). Then, the mixture is cooled to r.t., some ml of MeOH are added, and the solvent is evaporated *in vacuo*; yield 900 mg (58%) of **5**/**6**, separation by fractional crystallization from MeOH and CC.

1-[1-(4-Methoxyphenyl)-3-(3-methylbuta-1,3-dienyl)-2-oxo-4-phenylazetidin-3-yl]-4-phenyl-1,2,4-triazolidine-3,5-dione (**5**). R_f 0.25; 380 mg (25%) of **5**. Colorless crystals. M.p. 197° (dec., MeOH). IR: 3150–3090 (NH), 1787, 1740, 1705 (CO), 1655 (C=C). ^{1}H-NMR (300 MHz): 1.56 (br. *s*, Me); 3.50 (*s*, MeO); 4.71, 4.86 (2 br. *s*, $=CH_2$); 5.15 (*s*, Ph–C*H*); 5.50, 5.55 (2*d*, each J = 7.5, CH=CH); 6.5–7.3 (*m*, 14 arom. H, NH). 2D-H,H-COSY 45°: Relaxation delay: 1.000 s, acquisition time: 0.128 s, 16 repetitions. Anal. calc. for $C_{29}H_{26}N_4O_4$ (494.55): C 70.43, H 5.30, N 11.33; found: C 70.16, H 5.19, N 11.20.

1-{1-{[1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidin-3-ylidene]methyl}-2-methylprop-2-enyl}-4-phenyl-1,2,4-triazole-3,5-dione (**6**). R_f 0.18. IR: 3170 (NH), 1765, 1745, 1710 (CO), 1652 (C=C). ^{1}H-NMR (400 MHz): 1.15 (*s*, Me); 3.48 (*s*, MeO); 4.61, 4.67 (2 br. *s*, $=CH_2$); 4.79 (br. *d*, J = 10.5, CH–N); 5.32 (*d*, J = −1.5, Ph–C*H*); 6.22 (*dd*, J = 10.5, −1.5, =CH); 6.5–7.3 (*m*, 14 arom. H, NH). Anal. calc. for $C_{29}H_{26}N_4O_4$ (494.55): C 70.43, H 5.30, N 11.33; found: C 70.19, H 5.40, N 11.34.

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