124. 1,3-Cycloadditions to Highly Substituted, Strained Double Bonds: Spiro-β-lactams from α-Methylidene-β-lactams by Reactions with Diphenylnitrilimine, Acetonitrile Oxide, Nitrones, and Diazomethane

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Substituted dihydropyrazole-spiro-β-lactams and isoxazolidine-spiro-β-lactam derivatives are regio- and stereoselectively prepared by 1,3-cycloadditions between substituted α-methylidene-β-lactams and diazomethane, nitrones, or the *in-situ*-prepared dipoles 'diphenylnitrilimine' and acetonitrile oxide. These reactions represent examples for 1,3-cycloadditions to the highly substituted, strained double bonds of α-methylidene-β-lactams, and they need special experimental conditions as all reaction products are relatively unstable. Especially in solution, the reverse reaction is highly favoured. Regioselectivity and stereoselectivity of the reactions are elucidated mainly by NMR techniques such as 2D-INEPT, ATP, and NOE experiments.

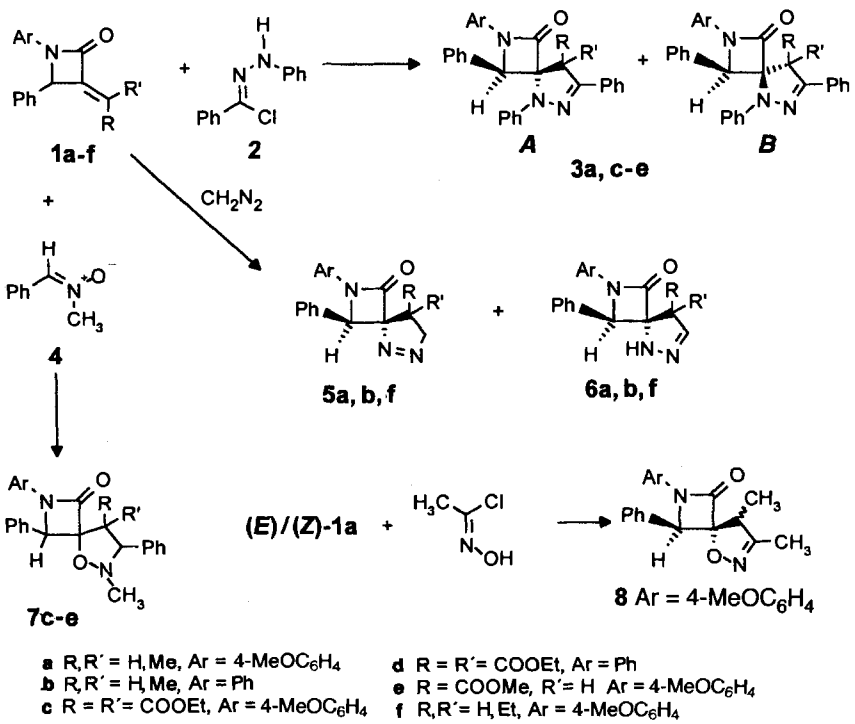
Introduction. – The 1,3-cycloaddition reactions present a valuable tool for the construction of five-membered heterocycles [1]. The intramolecular variation allows the synthesis of more complex structures [2]. *Huisgen* [3] described, *e.g.*, reactions between 1,3-dipoles and dipolarophiles with strained double bonds like cyclopentene or dicyclopentadiene and with olefines showing enhanced reactivity towards electron-rich 1,3-dipoles by conjugation with an electron-withdrawing group. In these reactions, the mainly used substrates were acrylates [3c]. The general concept was developed by *Huisgen* in the fifties [3] [4], and today most parameters controlling the reaction are known. Since the discovery of monolactams as potent antibiotics [5], the chemical modification of simple monocylic β-lactams gains more and more importance [6]. Previously, we have described the synthesis of β-lactams with a spiro[2.3] [7] or a spiro[3.5] structure [8]. In this paper, we report on the synthesis and properties of β-lactams with a spiro[3.4] structure. Some examples of the latter type, derived from reactions between methylidene derivatives of asparenomycine and penicillanic acid with acetonitrile oxide and diazomethane, have been described by other authors [9].

Results. – The substituted α-methylidene-β-lactams **1** were prepared by *Peterson* olefinations of the α-silylated β-lactams, as described by *Ruf* [10]. Lactams **1a** and **1b** were obtained as (*E*)/(*Z*)-mixtures which were separated into the isomers by flash chromatography (FC). From **1e**, we isolated only the (*E*)-isomer, and the (*E*)/(*Z*)-mixture **1f** was not separated. Diphenylnitrilimine, (= phenyl(phenylmethylidyne)-

[1]) Part of the Thesis of *A. S.*, University of Freiburg, 1995.

hydrazinium inner salt) was first prepared *in situ* by thermolysis of 2,5-diphenyl-1*H*-tetrazole [11] in anisol in the presence of (*E*)/(*Z*)-**1a**. No reaction product was detected. We recovered **1a** and isolated the dimer of the dipole, namely 1,4-dihydro-1,3,4,6-tetraphenyl-1,2,4,5-tetrazine [12]. To supress the dimerization of the dipole, *N*-phenylbenzenecarbohydrazonoyl chloride (**2**) was used as a precursor for the 'nitrilimine', and when the reaction with **1** was performed in boiling benzene in the presence of Et_3N [13], indeed the cycloaddition products of type **3** from (*E*)-**1a**, (*Z*)-**1a**, **1c**, **1d**, and **1e** were formed (*Scheme*). It is emphasized that, in contrast to the usually reported procedure, a solution of **2** was added to a solution of **1**, whereby the dimerization was suppressed. The reaction time varied between 25 and 30 days (!), and we concentrated the reaction mixture in intervals of 48 h to avoid dilution effects. Workup caused some problems, as in some solvents such as $CHCl_3$ the adducts **3** are not stable, as the cycloreversion reaction is favoured. As can be seen from the ^{1}H-NMR spectra, the adducts of type **3** are formed as mixtures of two diastereoisomers, the major isomer **A** and the minor isomer **B**, which we could not separate. The yields of isolated products varied between 3.6% (**3e**) and 58% (**3c**). Furthermore, we did not notice any significant difference in reaction time or field starting with the pure isomers, as from (*E*)-**1a** we obtained 20% of **3a**, and from (*Z*)-**1a** 22%. Obviously, the latter result is caused by the isomerization of (*Z*)- to (*E*)-**1a** in the presence of Et_3N. A similar isomerization is reported [14] for a benzylideneoxazolone derivative, and we found that (*Z*)-**1a** is completely converted into (*E*)-**1a** after 1 h in boiling benzene/Et_3N.

Scheme



a R,R′ = H, Me, Ar = 4-MeOC$_6$H$_4$
b R,R′ = H, Me, Ar = Ph
c R = R′ = COOEt, Ar = 4-MeOC$_6$H$_4$
d R = R′ = COOEt, Ar = Ph
e R = COOMe, R′ = H Ar = 4-MeOC$_6$H$_4$
f R,R′ = H, Et, Ar = 4-MeOC$_6$H$_4$

Acetonitrile oxide was obtained from freshly prepared acetohydroxamoyl chloride (= *N*-hydroxyethanimidoyl chloride) [9a]. This dipole showed a very limited reactivity towards the α-methylidene-β-lactams **1**. A successful reaction occurred only with **1a**, and both isomers (*E*)-**1a** and (*Z*)-**1a** yielded the product **8** (*Scheme*). The same product **8** was isolated applying the method of *Mukaiyama-Hoshino* [15]: Up to 10 equiv. of phenyl isocyanate and nitroethane were added to (*E*)/(*Z*)-**1a** in benzene solution, stirring was continued under reflux for 24 h, and the whole procedure was repeated for 10–15 times. However, even under these conditions, no reaction occurred with **1b** or **1c**. Finally, the silyl nitronates prepared from nitromethane or nitroethane [16] did not react with any of the β-lactams **1**.

A similar situation was found, when we tried to react nitrones with some of the β-lactams **1**. Compound **4** was the only nitrone which underwent reaction with **1c**, **1d**, and (*E*)-**1e** yielding acceptable amounts of the corresponding spiro compounds **7c–e** (*Scheme*). But also in these transformations, we could not use the normal procedure [17]. The addition of the nitrone had to be repeated and the reaction time prolonged to up to 15 days. Under these conditions, the yields of isolated products **7** reached 37% at best. When using the method of *Huisgen* and coworkers [18], none of our substrates **1** did react.

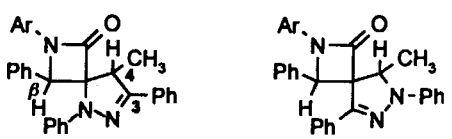
Finally, we tried to react **1** with diazomethane [19]. In contrast to **4**, diazomethane only reacted with **1a**, **b**, **f** yielding the corresponding spiro compounds **5a**, **b**, **f** and **6a**, **b**, **f** in *ca.* 20% yields.

All adducts are isolated as colourless crystals. They are relatively unstable, especially in solution ($CHCl_3$), the cycloreversion being highly favoured. The pyrazoline derivatives **3** are the only ones showing a fluorescence at λ 350 nm.

Stereochemistry and Discussion. – To the best of our knowlewdge, above described reactions are the first examples of 1,3-dipolar cycloadditions to the exocyclic C=C bond of monocyclic α-methylidene-β-lactams of type **1**. The regiochemistry of these additions depends on the orientation of the dipole to the C=C bond and allows in principal two orientations resulting in the regioisomers **I** and **II** as product of the reaction between **1a** and **2** (see *Fig. 1*).

The NMR data of addition product **3a** suggest that regioisomer **I** is formed from **1a**, and that the attack of the N-atom of the dipole has occurred essentially from the less hindered side of the β-lactam, *i.e.*, opposite to Ph–C(β) yielding the major isomer **A**. The ^{1}H-NMR spectra of **3a**, **c**, **d** clearly demonstrate the existence of diasteroisomer mixtures. Therefore, we postulate that the attack of the dipole opposite to Ph–C(β) is favoured (→ **A**); whereas the minor isomer **B** represents the product of an attack from the same side.

The structure of the isolated products was elucidated mainly by NMR spectroscopy. A 2D-INEPT-long-range experiment with **3a** shows no interaction of the sp^2-C-atom of the dihydropyrazole part (155.9 ppm) with



I II

Fig. 1. *Possible regioisomers of* **3a**. Ar = anisyl, arbitrary numbering.

H–C(β) of the β-lactam part, but a strong interaction with the H-atom and the Me protons of the dihydropyrazole part. The difference NOE experiment and the NOESY spectrum of **3a** do not exhibit any interactions between H–C(β) of the β-lactam part and the H-atom or Me group of the dihydropyrazole part, but an interaction between H–C(β) and aromatic protons.

The reactions of the electron-rich C=C bond of **1a, b, f** with diazomethane follow the same regioselectivity. We find only products from an attack of the N-atom from the side opposite to Ph–C(β) of the β-lactam. This is deduced from the coupling constants in the ^{1}H-NMR spectra. In a classical 1,3-dipolar cycloaddition, the reactivity of the components depends on the energetic situation of the frontier orbitals. Following this rule, we would expect diazomethane reacting with electron-poor double bonds. But as diazomethane reacts only with the electron-rich derivatives of **1**, we have to consider that either these reactions only look like cycloadditions or that some other additional effects intervene. One of these effects might be the electrophilic character of diazomethane, which could explain that diazomethane does not react with the electron-poor C=C bond in **1c, d, e**. Both tautomeric forms **5a, b, f** and **6a, b, f** are easily detected, their ratio depending on the solvent (see *Exper. Part*).

An additional electrophilic effect even would explain that in contrast to the reactions with diazomethane, the nitrone **4** only reacted with the electron-poor C=C bonds in **1c, d, e** yielding **7c, d, e**. From all these reactions, we isolated only one diastereoisomer. To prove the regioselectivity of the nitrone addition, ATP ^{13}C-NMR, and 2D-INEPT-long-range experiments were performed with **7c** and **7d**, confirming the selective formation of regioisomer **III** (*Fig. 2*). NOE Experiments show interaction of H–C(3) of the isoxazolidine moiety and of H–C(β) with aromatic protons, and of H–C(3) with the methyl group and the protons of the ester groups. These criteria are congruent only with the relative configuration as shown in **III**.

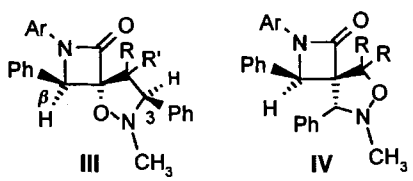


Fig. 2. *Possible regioisomers of* **7c** *and* **7d**. Arbitrary numbering.

The reaction of nitrone **4** yielding **7e** shows the same regiochemistry as those giving **7c** and **7d**, but the configuration of **7e** is different. From the measured NOEs (*Table*), we deduce that the attack of the dipole on **1e** has occurred from the side of Ph–C(β) of the β-lactam ring. We do not see any other possibility to explain the strong NOE effect between H–C(β) and the ester Me group. The NOE between H–C(4) and H–C(β) suggest that these protons are close together, while H–C(3) shows no interaction with these protons. As a result of these data we have to assume the structure of **7e** as given in *Fig. 3*.

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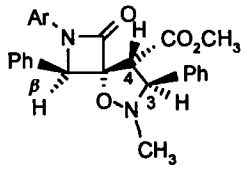

Fig. 3. *Relative configuration of* 7e. Arbitrary numbering.

Table. *NOEs Observed in the* ^{1}*H-NMR Spectrum* (300 MHz; $CDCl_3$) *of* 7e[a])

Irradiated H-atoms(s)	NOE at					
	MeN (δ 2.25)	CO_2Me (δ 3.66)	H–C(3) (δ 3.91)	H–C(4) (δ 4.08)	H–C(β) (δ 5.08)	arom. H (δ 6.7–7.5)
MeN (δ 2.25)		–	++	+	–	–
CO_2Me (δ 3.66)	–		–	–	++	–
H–C(4) (δ 4.08)	+	–	–		+	++
H–C(β) (δ 5.08)	–	++	–	+		++

[a]) Arbitrary numbering; + positive effect.

Experimental Part

1. *General.* Tetrahydrofuran (THF) was stored over KOH, then refluxed with Na/benzophenone, and distilled prior to use. Other solvents were dried/purified according to literature procedures. Lithium diisopropylamide (LDA) was obtained by mixing before use equimolar amounts of (i-Pr)$_2$NH and BuLi (15% in hexane) in THF at –78°. NH_4Cl soln.: 60 g/l NH_4Cl. Flash chromatography (FC): silica gel *60* (*Merck*, No. 9385, 230–400 mesh). Thin-layer chromatography (TLC): silica gel *60 F254*, (DC-Alufolien *Merck*, No. 5554); detection by UV and cerium(IV) reagent. $(Ce(SO_4)_2 \cdot 4\,H_2O$ (1 g) and phosphomolybdic(VI) acid (2.5 g) were dissolved in conc. H_2SO_4 (96%, 6 ml) and H_2O was added to give 100 ml). M.p: not corrected; *Kofler* hot stage, *Reichert AG*, Wien. IR Spectra (cm^{-1}): *Perkin-Elmer IR 841, IR 1310, Beckman IR 4240*; in KBr, if not noted otherwise. NMR Spectra: *Varian T60, Bruker WP80, WH90, WM200, WM250, Varian Unity 300* for ^{1}H; *Varian Unity 300* (75.43 MHz) für ^{13}C; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz; values from 300-MHz spectra in $CDCl_3$, if not noted otherwise. MS (70 eV): *Finnigan MAT 312*. Elemental analyses: Pharmazeutisches Institut der Universität Freiburg or Chemisches Laboratorium der Universität Freiburg.

2. *Starting Materials. 3-Ethylidene-1-(4-methoxyphenyl)-4-phenylazetidin-2-one* (**1a**). From 1-(4-methoxyphenyl)-4-phenylazetidin-2-one (3.25 g, 0.01 mol) and MeCHO (4.4 g, 0.1 mol) according to the general procedure described in [20]. Separation of isomers by FC(CH_2Cl_2). (*E*)/(*Z*)-**1a**: Anal. calc. for $C_{18}H_{17}NO_2$ (279.34): C 77.39, H 6.13, N 5.02; found: C 77.55, H 5.91, N 5.34.

(*E*)-**1a**: 0.72 g (26%). Colourless crystals. R_f 0.16. M.p. 138° (CH_2Cl_2). IR: 3068, 2969, 2928, 2839 (CH), 1725 (CO). ^{1}H-NMR (80 MHz): 1.55 (*d*, *J* = 7.8, *Me*CH=C); 3.70 (*s*, MeO); 5.36 (*d*, *J* = – 2.0, H–C(4)); 6.23 (*dq*, *J* = 7.8, –2.0, MeC*H*=C); 6.55–7.6 (*m*, 9 arom. H).

(*Z*)-**1a**: 0.40 g (14%). Colourless crystals. R_f 0.26. M.p. 135° (CH_2Cl_2). IR: 3079, 3060, 3031, 2984, 2959, 2937, 2913, 2838 (CH), 1720 (CO). ^{1}H-NMR (80 MHz): 2.05 (*d*, *J* = 7.8, *Me*CH=C); 3.70 (*s*, MeO); 5.23 (*d*, *J* = – 2.0, H–C(4)); 5.57 (*dq*, *J* = 7.8, –2.0, MeC*H*=C); 6.62–7.58 (*m*, 9 arom. H).

3-Ethylidene-1,4-diphenylazetidin-2-one (**1b**). From 1,4-diphenylazetidin-2-one (3.0 g, 0.01 mol) and MeCHO (4.4 g, 0.1 mol). Separation of isomers by FC (CH_2Cl_2). (*E*)/(*Z*)-**1b**: Anal. calc. for $C_{17}H_{15}NO$ (249.32): C 81.90, H 6.06, N 5.62; found: C 81.83, H 6.08, N 5.45.

(*E*)-**1b**: 0.27 g (18%). Colourless crystals. R_f 0.17. M.p. 156° (CH_2Cl_2). IR: 3056, 3027, 2980, 2943, 2919, 2850 (CH), 1737 (CO). ^{1}H-NMR (80 MHz): 1.54 (*d*, *J* = 7.9, *Me*CH=C); 5.38 (*d*, *J* = – 1.8, H–C(4)); 6.27 (*dq*, *J* = 7.9, –1.8, MeC*H*=C); 6.75–7.5 (*m*, 10 arom. H).

(*Z*)-**1b**: 0.21 g (14%). Colourless crystals. R_f 0.31. M.p. 151° (CH_2Cl_2). IR: 3032, 2985, 2944, 2911, 2854 (CH), 1718 (CO). ^{1}H-NMR (80 MHz): 1.80 (*d*, *J* = 7.9, *Me*CH=C); 5.28 (*d*, *J* = – 1.8, H–C(4)); 5.57 (*dq*, *J* = 7.9, –1.8, MeC*H*=C); 6.75–7.5 (*s*, 10 arom. H).

Diethyl 2-[1-(Methoxyphenyl)-2-oxo-4-phenylazetidin-3-ylidene]propanedioate (**1c**) *and Diethyl 2-[2-Oxo-1,4-diphenylazetidin-3-ylidene]propanedioate* (**1d**). See [20].

Methyl (E)-2-[1-(4-Methoxyphenyl-2-oxo)-4-phenylazetidin-3-ylidene]acetate (**1e**). See [7b].

1-(4-Methoxyphenyl)-4-phenyl-3-propylideneazetidin-2-one (**1f**). See [20].

N-*Phenylbenzenecarbohydrazonoyl Chloride* (**2**). See [3c].

3. *Reaction of* **1** *with 'Diphenylnitrilimine'. General Procedure.* Under N_2, **1** (0.002 mol) and Et_3N (0.002 mol) in benzene (40 ml) are heated to the boiling point. Then, a soln. of **2** (0.46 g, 0.002 mol) in benzene (20 ml) is dropwise added. After 24 h, more Et_3N (0.002 mol) and **2** (0.002 mol) in benzene are added. This procedure is repeated until the reaction is complete (TLC control). To avoid dilution effects, concentration *in vacuo* is recommended in intervals of 48 h. Finally, the solvent is evaporated at r.t. the residue dissolved in a few ml of AcOEt, this soln. washed with H_2O (3 ×), the combined aq. phase extracted with AcOEt, and the combined org. extract dried ($MgSO_4$) and evaporated. The residue is purified as indicated.

2-(4-Methoxyphenyl)-8-methyl-3,5,7-triphenyl-2,5,6-triazaspiro[3.4]oct-6-en-1-one (**3a**). From (*E*)- or (*Z*)-**1a** (0.56 g, 0.002 mol) and **2** (20 equiv.). The residue is 3 times recrystallized from MeOH, and the colourless crystals are dissolved in benzene (the brown crystals (1,4-dihydro-1,3,4,6-tetraphenyl-1,2,4,5-tetrazine) should not be dissolved!). After separation of the brown crystals, the filtrate is evaporated: 0.214 g (22.6%) and 0.185 g (20%) of **3a** from (*E*)- and (*Z*)-**1a**, resp. Colourless, fluorescent (350 nm) crystals (6.5:1 isomers mixture). M.p. 214° (MeOH). IR: 3059 (CH), 1737 (CO), 1597, 1512 (arom. C–C). ^{1}H-NMR (300 MHz, (D_6)DMSO; signals of the minor isomer in italics): *0.29*, 0.37 (*d*, *J* = 7, Me–C(8)); 3.64, *3.69* (*s*, MeO); 4.03, *5.02* (*q*, *J* = 7, H–C(8)); *5.66*, 5.71 (*s*, H–C(3)); 6.73–7.8 (*m*, 19 arom. H). ^{13}C-NMR ((D_6)DMSO): 10.88 (Me); 41.56 (C(8)); 55.02 (MeO); 61.56 (C(3)); 88.47 (C(4)); 114.28–143.93 (arom. C); 155.80, 155.93 (MeO–*C*, C(7)); 163.62 (C(1)). Anal. calc. for $C_{31}H_{27}N_3O_2$ (473.59): C 78.62, H 5.75, N 8.87; found: C 78.34, H 5.84, N 8.95.

Diethyl 2-(4-Methoxyphenyl)-1-oxo-3,5,7-triphenyl-2,5,6-triazaspiro[3.4]oct-6-ene-8,8-dicarboxylate (**3c**). From **1c** (0.82 g, 0.002 mol) and **2** (25 equiv.): 0.74 g (58% of **3c**). Colourless, fluorescent (350 nm) crystals (2:1 isomer mixture). M.p. 184° (MeOH). IR: 3060, 2980, 2940, 2910, 2840 (CH), 1765, 1740 (CO), 1595, 1510 (arom. C–C). ^{1}H-NMR (300 MHz, (D_6)DMSO, signals of the minor isomer in italics). 0.55, *0.75* (*t*, *J* = 7, Me); *1.15*, 1.21 (*t*, *J* = 7, Me); 2.99, 3.07, *3.18*, *3.28* (*dq*, *J* = 7, 10.5, CH_2); *3.64*, 3.67 (*s*, MeO); *4.25*, 4.41 (*dq*, *q*, *J* = 7, *10.5*, CH_2); 5.32, *5.60* (*s*, H–C(3)); 6.61–7.62 (*m*, 19 arom. H). ^{13}C-NMR ((D_6)DMSO): 12.57, 12.81, 13.51, 13.79 (Me); 55.20 (MeO); 61.50, 61.97 (C(3)); 62.39 62.77, 63.62, 66.73 (CH_2); 88.90 (C(4)); 114.55–142.53 (arom. C); 143.29, 144.84 (C(8)); 156.29, 156.43 (MeO–*C*, C(7)); 161.21, 161.41, 161.96, 163.74, 164.70, 165.19 (CO). Anal. calc. for $C_{36}H_{33}N_3O_6$ (603.69): C 71.63, H 5.51, N 6.96; found: C 71.40, H 5.49, N 6.99.

Diethyl 1-Oxo-2,3,5,7-tetraphenyl-2,5,6-triazaspiro[3.4]oct-6-ene-8,8-dicarboxylate (**3d**). Form **1d** (0.758 g, 0.002 mol) and **2** (30 equiv.): 0.22 g (19%). Colourless, fluorescent (350 nm) crystals (2.5:1 isomer mixture). M.p. 196° (MeOH). IR: 3070, 2980, 2930, 2860 (CH), 1755 (CO), 1598 (arom. C–C). ^{1}H-NMR (200 MHz, CD_3OD; signals of the minor isomer in italics): 0.65, *0.87* (*t*, *J* = 7, Me); *1.27*, 1.45 (*t*, *J* = 7, Me); 3.10 (*m*, CH_2); *4.31*, 4.48 (*q*, *J* = 7, CH_2); 5.64, *5.88* (*s*, H–C(3)); 6.90–7.82 (*m*, 20 arom. H). Anal. calc. for $C_{35}H_{31}N_3O_5$ (573.66): C 73.28, H 5.45, N 7.33; found: C 73.05, H 5.65, N 7.13.

Methyl 2-(4-Methoxyphenyl)-1-oxo-3,5,7-triphenyl-2,5,6-triazaspiro[3.4]oct-6-ene-8-carboxylate (**3e**). From **1e** (0.647 g, 0.002 mol) and **2** (45 equiv.). The residue is 3 times recrystallized from MeOH and the mixture of crystals (brown and colourless) washed with petroleum ether until the brown crystals are dissolved: 0.037 g (3.6%) of **3e**. Colourless, fluorescent (350 nm) crystals. M.p. 207° (MeOH). IR: 3058, 2953, 2837 (CH), 1751 (CO), 1597, 1512 (arom. C–C). ^{1}H-NMR: 2.93 (*s*, COOMe); 3.74 (*s*, MeO); 5.12 (*s*, H–C(8)); 5.43 (*s*, H–C(3)); 6.74–7.8 (*m*, 19 arom. H). EI-MS (70 eV): 517 (6, M^+), 427 (3, $[M - PhCH]^+$), 368 (13, $[M - MeOC_6H_4NCO]^+$), 309 (100). HR-MS: 517.2018 ($C_{32}H_{27}N_3O_4^+$; calc. 517.58).

4. *Reactions with Diazomethane. General Procedure.* Into a soln. of **1** (0.002 mol) in CH_2Cl_2 (50 ml) at 0°, CH_2N_2 (0.01 mol) (prepared from *Diazald*®) is transferred *via* a *Teflon* hose. The mixture is stirred for 8 h at 0°, then another portion of CH_2N_2 is added. This procedure is repeated (*ca.* 10 times) until the reaction is completed (TLC). Then, the solvent is evaporated at r.t. and the residue purified by FC (CH_2Cl_2).

2-(4-Methoxyphenyl)-8-methyl-3-phenyl-2,5,6-triazaspiro[3.4]oct-5-en-1-one (**5a**) *and 2-(4-Methoxyphenyl)-8-methyl-3-phenyl-2,5,6-triazaspiro[3.4]oct-6-en-1-one* (**6a**). From **1a**, 0.14 g (22%) of **5a**/**6a** 6:1. Colourless crystals. R_f 0.1. M.p. 156–158° (dec., CH_2Cl_2). IR: 3063, 2961, 2932, 2835 (CH), 1740 (CO), 1585, 1512 (arom. C–C). Anal. calc. for $C_{19}H_{19}N_3O_2$ (321.39): C 71.00, H 5.95, N 13.07; found: C 70.79, H 6.06, N 13.00.

5a: ^{1}H-NMR (250 MHz, $CDCl_3$): 0.00 (*d*, *J* = 7, Me–C(8)); 2.55 (*m*, *J* = 7, 6, 1, H–C(8)); 3.69 (*s*, MeO); 4.39 (*dd*, *J* = 16.5, 6, 1 H–C(7)); 4.51 (*dd*, *J* = 16.5, 1, 1H–C(7); 6.05 (*s*, H–C(3)); 6.69–7.55 (*m*, 9 arom. H).

6a: ^{1}H-NMR (250 MHz, $CDCl_3$): 1.08 (*d*, *J* = 7, Me–C(8)); 3.72 (*s*, MeO); 4.08 (*dq*, *J* = 7, 1.2, H–C(8)); 5.42 (*s*, H–(3)); 6.99–7.49 (*m*, 9 arom. H, H–C(5), H–C(7)).

8-Methyl-2,3-diphenyl-2,5,6-triazaspiro[3.4]oct-5-en-1-one (**5b**) *and 8-Methyl-2,3-diphenyl-2,5,6-triazaspiro[3.4]oct-6-en-1-one* (**6b**). From **1b**, 0.12 g (21%) of **5b**/**6b** 2.5:1. Colourless crystals. R_f 0.15. M.p. 163–167° (dec., CH_2Cl_2). IR: 3032, 2932 (CH), 1744 (CO), 1596, 1535, 1492 (arom. C–C). CI-MS (isobutane, 70 eV): 292 (100, $[M+1]^+$), 264 (50, $[M+1-N_2]^+$), 250 (38, $[M+1-CH_2N_2]^+$), 229 (15, $[M+C_4H_9-PhNCO]^+$), 182 (21, $[PhN{=}CHPh+H]^+$), 173 (54, $[M+H-pHNCO]^+$). HR-MS: 291.1366 ($C_{18}H_{17}N_3O$; + calc. 291.36).

5b: ^{1}H-NMR: 0.005 (*d*, *J* = 7, Me–C(8)); 2.56 (*m*, *J* = 7, 6.1, 0.98, H–C(8)); 4.40 (*dd*, *J* = 16.6, 6.1, 1H–C(7)); 4.52 (*dd*, *J* = 16.6, 0.98, 1H–C(7)); 6.1 (*s*, H–C(3)); 6.99–7.49 (*m*, 10 arom. H).

6b: ^{1}H-NMR: 0.255 (*d*, *J* = 7.3, Me–C(8)); 3.22 (*dq*, *J* = 7.3, 1.2, H–C(8)); 5.19 (*s*, H–C(3)); 6.99–7.49 (*m*, 10 arom. H, H–C(5), H–C(7)).

8-Ethyl-2-(4-methoxyphenyl)-3-phenyl-2,5,6-triazaspiro[3.4]oct-5-en-1-one (**5f**) *and 8-Ethyl-2-(4-methoxyphenyl)-3-phenyl-2,5,6-triazaspiro[3.4]oct-6-en-1-one* (**6f**). From **1f**, 0.09 g (13%) of **5f**/**6f** 3:1. Colourless crystals. R_f 0.185. M.p. 163–167° (dec., CH_2Cl_2). IR: 2934, 2837 (CH), 1736 (CO), 1611, 1584, 1513, 1455 (arom. C–C). ^{1}H-NMR (signals of the minor isomer in italics): 0.15, *0.45* (*m*, CH_2); 0.32, *0.68* (*t*, *J* = 7.2, Me); *0.85*, 2.54 (*m*, H–C(8)); 3.73, *3.78* (*s*, MeO); *4.19*, 4.39 (*dd*, *J* = 16.8, 6.6, 1H–C(7)); *4.57*, 4.63 (*dd*, *J* = 16.8, 1.2, 1H–C(7)); *5.57*, 6.05 (*s*, H–C(3)); 6.71–7.6 (*m*, 9 arom. H).

5. *Cycloadditions with* N-*(phenylmethylidene)methanamine* N-*Oxide* (**4**). *General Procedure.* Under N_2, **1** (0.002 mol) and **4** (270 mg, 0.002 mol) in toluene (50 ml) are refluxed for 12 h. Then more **4** (270 mg) is added and refluxing continued. This procedure is repeated until control disappearance of **1** (TLC control). Then, the solvent is evaporated and the residue purified by FC.

Diethyl 2-(4-Methoxyphenyl)-6-methyl-1-oxo-3,7-diphenyl-5-oxa-2,6-diazaspiro[3.4]octane-8,8-dicarboxylate (**7c**). From **1c** (0.82 g, 0.002 mol) and **4** (30 equiv.). FC (Et_2O/petroleum ether 1:1; R_f 0.45) gives 0.29 g (26%) of **7c**. Colourless crystals. M.p. 142° (Et_2O/petroleum ether 1:1). IR: 2924, 2853 (CH), 1762, 1745 (CO), 1584, 1511 (arom. C–C). ^{1}H-NMR: 0.81 (*t*, *J* = 7, Me); 0.96 (*t*, *J* = 7, Me); 2.60 (*s*, MeN); 3.67 (*dq*, *J* = 7, 10, CH_2); 3.72 (*s*, MeO); 3.98 (*dq*, *J* = 7, 10, CH_2); 4.1 (*q*, *J* = 7, CH_2); 4.76 (*s*, H–C(7)); 5.53 (*s*, H–C(3)); 6.74–7.60 (*m*, 14 arom. H). ^{13}C-NMR: 19.21, 19.42 (Me); 50.23 (MeN); 61.27 (MeO); 67.75, 68.22 (CH_2); 72.94 (C(7)); 77.82 (C(8)); 82.55 (C(3)); 99.45 (C(4)); 120.20–134.76 (arom. CH); 136.32, 139.35, 139.84 (arom. C); 162.29 (MeO–*C*); 170.03 (NCO); 171.76, 171.84 (CO). EI-MS (70 eV): 544 (30, M^+), 409 (33, $[M-PhCHN(Me)O]^+$), 395 (9, $[M-MeOC_6H_4NCO]^+$), 364 (6, $[M-PhCHN(Me)O-EtO]^+$), 211 (100). HR-MS: 544.2197 ($C_{31}H_{32}N_2O_7^+$; calc. 544.60).

Diethyl 6-Methyl-1-oxo-2,3,7-triphenyl-5-oxa-2,6-diazaspiro[3.4]octane-8,8-dicarboxylate (**7d**). From **1d** (0.758 g, 0.002 mol) and **4** (35 equiv.). The residue is extracted with Et_2O. Purification by FC (Et_2O/CH_2Cl_2 1:1, R_f 0.37) gives 0.39 g (37%) of **7d**. Colourless crystals. M.p. 171° (Et_2O/CH_2Cl_2 1:1). IR: 3061, 3032, 2983, 2937, 2875 (CH), 1757, 1729 (CO), 1596, 1496 (arom. C–C). ^{1}H-NMR: 0.81 (*t*, *J* = 7, Me); 0.94 (*t*, *J* = 7, Me); 2.63 (*s*, MeN); 3.62 (*dq*, *J* = 7, 10, CH_2); 4.00 (*dq*, *J* = 7, 10, CH_2); 4.10 (*q*, *J* = 7, CH_2); 4.77 (*s*, H–C(7)); 5.09 (*s*, H–C(3)); 6.94–7.67 (*m*, 15 arom. H). Anal. calc. for $C_{30}H_{30}N_2O_6$ (514.58): C 70.02, H 5.88, N 5.44; found: C 69.90, H 5.88, N 5.33.

Methyl 2-(4-Methoxyphenyl)-6-methyl-1-oxo-3,7-diphenyl-5-oxa-2,6-diazaspiro[3.4]octane-8-carboxylate (**7e**). From **1e** (0.647 g, 0.002 mol) and **4** (35 equiv.). The residue is extracted with Et_2O. Purification by FC (Et_2O/CH_2Cl_2 1:1; R_f 0.68) gives 0.303 g (33%) of **7e**. Colourless crystals. M.p. 178° (Et_2O/CH_2Cl_2 1:1). IR: 3057, 3005, 2956, 2921, 2852 (CH), 1738 (CO), 1601, 1584, 1510 (arom. C–C). ^{1}H-NMR: 2.25 (*s*, MeN); 3.66 (*s*, CO_2Me); 3.72 (*s*, MeO); 3.91 (*d*, *J* = 10.2, H–C(7)); 4.08 (*d*, *J* = 10.2, H–C(8)); 5.08 (*s*, H–C(3)); 6.74–7.52 (*m*, 14 arom. H). ^{13}C-NMR: 43.21 (C(8)); 52.43 (MeN); 55.37 (MeO), 59.50 (MeO); 66.46 (C(7)); 75.09 (C(3)); 91.42 (C(4)); 114.35–135.58 (arom. C); 156.47 (MeO–*C*); 164.66 (NCO); 169.75 (CO). EI-MS (70 eV): 458 (14, M^+), 430 (3, $[M-CO]^+$), 427 (2, $[M-CO_2Me]^+$), 323 (5, $[M-CO-PhCHN(Me)O]^+$), 211 (100). HR-MS: 458.1836 ($C_{27}H_{26}N_2O_5^+$ calc. 458.51).

2-(4-Methoxyphenyl)-7,8-dimethyl-3-phenyl-5-oxa-2,6-diazaspiro[3.4]oct-6-en-1-one (**8**). *a*) At −30°, a soln. of acetaldehyde oxime (0.59 g, 10 mmol) in $CHCl_3$ (30 ml) is saturated with Cl_2, and the excess of Cl_2 is blown out by N_2 (*Soln. I*). This soln. is added dropwise and with stirring to a cold soln. (0°) of (*E*)/(*Z*)-**1a** (0.559 g, 0.002 mol) and Et_3N (0.71 g, 10 mmol) in $CHCl_3$ (20 ml). The mixture is stored at 5° for 60 h, then another equiv. of *Soln. I* is added. The procedure is repeated 5 times. To avoid dilution effects, concentration *in vacuo* (r.t.) is recommended in intervals of 120 h. Finally, the mixture is washed 3 times with H_2O (70 ml) and once with sat. NaCl soln. (50 ml). The org. layer is dried ($MgSO_4$) and evaporated *in vacuo* (r.t.). The residue is purified by FC (CH_2Cl_2):40 mg (5.7%) of **8**.

b) Nitroethane (0.75 g, 0.01 mol) and Et_3N (10 drops) are dissolved in benzene (15 ml) (*Soln. II*). This soln. is added to a soln. of phenyl isocyanate (2.38 g, 0.02 mol) and (*E*)/(*Z*)-**1a** (0.559 g, 0.002 mol) in benzene (25 ml). The mixture is stirred at r.t. for 1 h, then refluxed for 23 h. After cooling to r.t., phenyl isocyanate (2.38 g,

0.02 mol) and more *Soln. II* (15 ml) are added, and stirring and refluxing are repeated. This procedure is repeated 15 times. To avoid dilution effects, concentration *in vacuo* (r.t.) is recommended in intervals of 48 h. Finally, after cooling to r.t., the precipitate is separated, the soln. evaporated *in vacuo*, and the residue purified by FC: 35 mg (5.2%) of **8**. Colourless crystals. R_f 0.02. M.p. 215° (CH_2Cl_2). IR: 3064, 2931 (CH), 1744 (CO), 1584, 1512 (arom. C–C). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.36 (*d*, J = 7, Me); 1.96 (*s*, Me); 3.28 (*q*, J = 7, H–C(8)); 3.72 (*s*, MeO); 5.35 (*s*, H–C(3)); 6.6–7.65 (*m*, 9 arom. H). Anal. calc. for $C_{20}H_{20}N_2O_3$ (336.39): C 71.41, H 5.99, N 8.33; found: C 70.68, H 6.13, N 8.34.

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