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Regio- and Stereoselectivity in the 1,3-Dipolar Cycloaddition of C,N-Diarylnitrones to 3,3-Methylene-5,5-dimethyl-2-pyrrolidinone

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Summary. Regio- and stereoselectivity of the nitrone cycloaddition with 3,3-methylene-5,5-dimethyl-2-pyrrolidinone ((1) is discussed. Nitrones react regioselectively with **1** to give a mixture of diastereoisomeric spiro-cycloadducts **3** and **4**, in which **3** always dominates. Both **3** and **4** result from the approach which binds the carbon of the nitrone with the exocyclic carbon of **1** and the oxygen to the spiro carbon. The structure and steric configuration of the adducts have been assigned on the basis of ^{1}H- and ^{13}C-NMR spectroscopy, mainly by nuclear Overhauser effect difference spectroscopy. AM1 calculations of the reactants were performed, the regio- and stereochemistry of the cycloaddition seems to be controlled by steric effects.

Keywords. 1,3-Dipolar cycloaddition of nitrones; 3,3-Methylene-5,5-dimethyl-2-pyrrolidinone; Regio- and stereoselectivity of 1,3-dipolar cycloaddition.

Regio- und Stereoselektivität bei der 1,3-dipolaren Cycloaddition von C,N-Diarylnitronen an 3,3-Methylen-5,5-dimethyl-2-pyrolidinon

Zusammenfassung. Es wird die Regio- und Stereoselektivität der Cycloaddition von Nitronen an 3,3-Methylen-5,5-dimethyl-2-pyrolidinon (**1**) diskutiert. Nitrone reagieren mit **1** regioselektiv zu einer Mischung von diastereomeren Spirocycloaddukten **3** und **4**, wobei **3** stets dominierend ist. Sowohl **3** als auch **4** resultieren aus der gleichen Reaktionsanordnung unter Bindung des Nitron-Kohlenstoffatoms an das exocyclische Kohlenstoffatom von **1** und des Sauerstoffatoms an den Spiro-Kohlenstoff. Die Stereochemie der Addukte wurde auf Basis von ^{1}H- und ^{13}C-NMR-Spektroskopie, insbesondere aus Differenz-Nuclear-Overhauser-Messungen, abgeleitet. Es wurden auch AM1-Rechnungen durchgeführt. Die Regio- und Stereochemie der Cycloaddition scheint von sterischen Effekten bestimmt zu sein.

Introduction

The 1,3-dipolar cycloaddition reaction is one of the most useful reactions for the synthesis of heterocyclic compounds [1]. It has a nearly singular capability of

establishing large numbers of stereochemical centers in one synthetic step. In this line, an impressive effort has been devoted to the synthetic application of the cycloaddition of nitrones to alkenes to give isoxazolidines [2–4]. The ability to utilize nitrone cycloadditions in organic synthesis depends heavily on understanding the factors which determine the regiochemistry of the reaction.

With our efforts [5–9] to utilize heterocyclic compounds as dipolarophile component in 1,3-dipolar cycloaddition we have recently demonstrated [10] that nitrile oxides react with 3,3-methylene-5,5-dimethyl-2-pyrrolidinone (**1**) to produce exclusively isoxazoline regioisomers **7**. With the aim of expanding the synthetic utility of **1**, we report [11] now on the regio- and stereochemical features associated with the cycloaddition of several aryl nitrones to **1**, together with quantum mechanical calculations using the AM1 method.

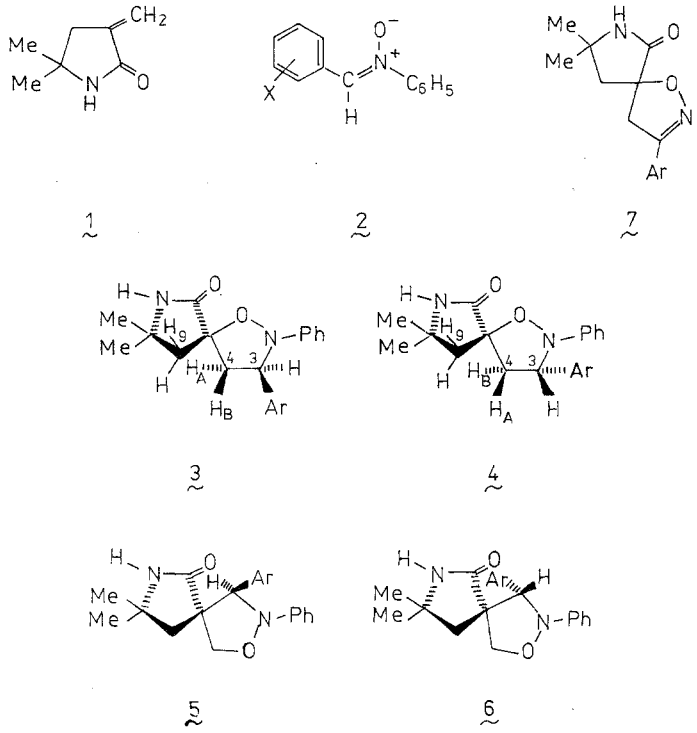
Results and Discussion

1,3-Dipolar cycloaddition of C-(*X*-phenyl)-N-phenyl nitrones **2** (where *X* is H, 2-Cl, 4-Cl, 2-F, 3-NO_2, 4-CH_3, and 4-OCH_3) and **1** in toluene at 110°C afforded the isoxazolidines **3** and **4** as a mixture of diastereoisomers, with the predominance of the isomer **3** (Table 1). Cycloaddition of nitrones **2** (where *X* is 2,4-diCl, 2-NO_2, and 4-NO_2) with **1** gave exclusively a single isoxazolidine **3**.The crude residue was chromatographically separated, and cycloadducts **3a–3k** as well as **4a** and **4j** could be obtained in pure form. NMR analysis of the crude mixture permitted a determination of the ratio of the epimers **3** and **4** present in the original reaction mixture. There are four possible adducts of **1** and arylnitrones **2** (compare the formula scheme); two regioisomeric pairs of two diastereoisomers **3**, **4** and **5**, **6**. The distinction between these possibilities was possible by spectroscopic data. In the NMR spectra of **3** and **4** an ABX system pertaining to the two hydrogens in position 4 and to the one in position 3 is present. This excludes the possibility that this is a mixture of regioisomers **5** or **6** and proves that both isolated adducts **3** and **4** result

Table 1. 2-Phenyl-3-(*X*-phenyl)-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro-[4,4]-non-2-enes

Compound	*X*	M.p. (°C)	Yield (%)	Formula[a]	M.w.	Ratio 3:4
3a	H	181–183	76	$C_{20}H_{22}N_2O_2$	322.40	80:20
4a	H	254–255	19	$C_{20}H_{22}N_2O_2$	322.40	
3b	2-Cl	186–188	73	$C_{20}H_{21}N_2O_2Cl$	356.84	81:19
3c	4-Cl	173–175	62	$C_{20}H_{21}N_2O_2Cl$	356.84	83:17
3d	2,4-Cl_2	183–184	60	$C_{20}H_{20}N_2O_2Cl_2$	391.29	100:0
3e	2-F	178–180	70	$C_{20}H_{21}N_2O_2F$	340.39	86:14
3f	2-NO_2	157–158	44	$C_{20}H_{21}N_3O_4$	367.39	100:0
3g	3-NO_2	182–183	73	$C_{20}H_{21}N_3O_4$	367.39	86:14
3h	4-NO_2	185–187	87	$C_{20}H_{21}N_3O_4$	367.39	100:0
3i	4-CH_3	193–195	40	$C_{21}H_{24}N_2O_2$	336.42	80:20
3j	4-OCH_3	165–166	78	$C_{21}H_{24}N_2O_3$	352.42	82:18
4j	4-OCH_3	257–258	10	$C_{21}H_{24}N_2O_3$	352.42	

[a] Satisfactory microanalyses obtained: C±0.30, H±0.25, N±0.25



from the same kind of approach between nitrone **2** and dipolarophile **1**, namely that which binds the carbon of the nitrone with the exocyclic carbon of the methylene group of **1** and the oxygen to the spiro carbon. The NMR spectrum of the regioisomers **5** or **6** would have a singlet for H-3 and an AB system for the two C-4 hydrogens.

The fact that the cycloaddition is regiospecific, affording only two isomers both with a 5-spiroisoxazolidine structure, is further supported by the chemical shift of the adjacent spiro-C carbon (C-5 $\delta \sim 85$ ppm) indicating a strong shielding influence of the spiroheterocyclic ring on the 5-position of the isoxazolidine, together with the expected value for C-4. The alternative regioisomeric cycloadducts **5** and **6** are not expected to show signals at this chemical shift value. A similar regioselectivity was observed in the cycloaddition of nitrones to methylenecycloalkanes [12–15].

It was a critical point to establish the configurations of the cycloadducts **3** and **4** unambiguously. In contrast to many other examples [16, 17] the stereochemistry

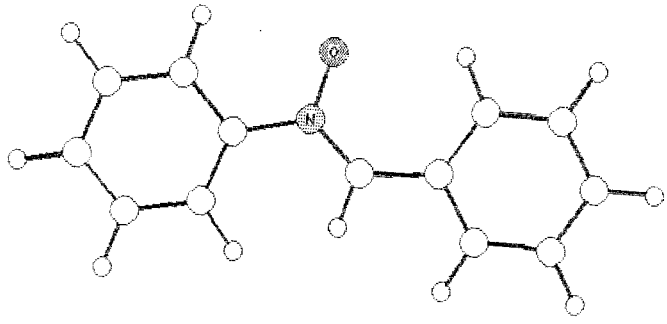


Fig. 1. Optimized geometry for C,N-diphenylnitrone **2** (AM1)

Table 2. Relevant electronic parameters of **1** and **2**

Molecule	E_{HOMO} (eV)	E_{LUMO} (eV)	HOMO		LUMO	
			Cα/O	Cβ/C	Cα/O	Cβ/C
1	−9.94	0.38	0.18	0.20	0.52	−0.67
2	−8.40	−0.72	0.50	−0.48	0.27	0.36

cannot be deduced from couplings H-3-H_A-4 and H-3-H_B-4, since these are very similar in both adducts. Therefore, the stereochemical assignment in compounds **3** and **4** was based on nuclear Overhauser effect difference spectroscopy which was used for isoxazolidines [18]. There is strong evidence that nitrones derived from aromatic aldehydes possess a configuration in which the C-aryl and N-phenyl groups are in a *trans* relationship [19]. In the dominant compounds **3** the high-field proton H_B-4 (*cis* to 3-aryl, [20]) shows a NOE with the H-9 proton, in the stereoisomers **4** a NOE between the low-field proton H_A-4 (*trans* to 3-aryl) and the H-9 proton is observed. In accord with this assignment, only a NOE between H-3 and H-9 could be detected in compound **4**, the corresponding NOE in **3** was absent.

The NMR-results are in general accord with earlier observations that the most electron-deficient dipolarophiles undergo cycloaddition with nitrones to give 5-substituted isoxazolidines [21, 22]. On the other hand, it was reported that very electron deficient dipolarophiles as well as some methylenecycloalkanes gave significant amounts of 4-substituted isoxazolidines. The cycloaddition of C-phenyl-N-methylnitrone to methylenecyclopropane gave a mixture of the two regioisomers in a 70:30 ratio [13, 14]. In order to rationalize the exclusive regioselectivity of these cycloadditions we have performed an FMO analysis of the calculated (AM1) [23–25] frontier orbitals. An optimized geometry for C,N-diphenylnitrone **2** is shown in Fig. 1; that of **1** was published previously in Ref. [10]. Some relevant results of calculations are summarized in Table 2. Inspection of frontier orbital energies shows that the interaction **1**–**2** is governed by the HOMO dipole.

According to the FMO theory, regioselectivity is governed predominantly by orbital coefficients at the double bond and by those at the terminal atoms of the

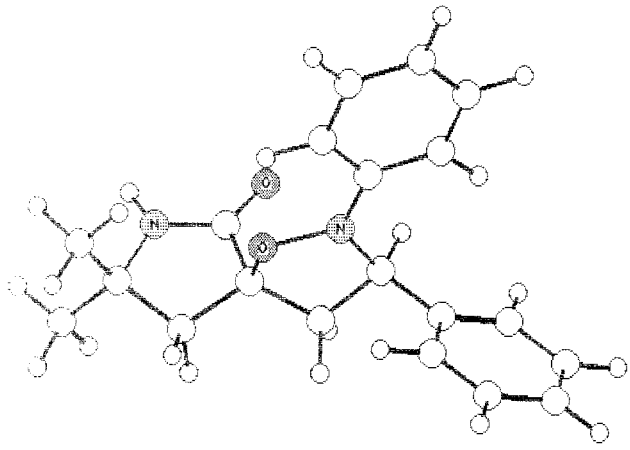


Fig. 2. Optimized geometry for cycloadduct **3** (MM 2)

dipole [21–24]. However, HOMO coefficients at both carbon and oxygen terminals of the dipole have almost the same value, so that an FMO analysis is not suited to furnish any arguments to the regioselectivity of the reaction. We therefore tried to assess the relative thermodynamic stability of the possible products **3–6**. Because of the large size of the molecules (too large for AM1) we resorted to the molecular mechanics program MM 2 [26] which was used to optimize the geometries of all four products **3–6**. The calculated energy differences (in $kJ\,mol^{-1}$) are in the following order (the energy of the most stable structure as reference):

$$E_3 = 0, \qquad E_4 = 15.4, \qquad E_5 = 113.2, \qquad E_6 = 123.6.$$

The calculation showed that products **3** and **4**, in which the dipole oxygen is bound to the carbon, are the more stable ones; structure **3** is more stable by a narrow margin, due to the advantageous conformational arrangement of its phenyl groups (Fig. 2). The regiochemistry of **3** and **4** is also favourable for steric reasons. The van der Waals nonbonding interaction energies should be very large in the regioisomers **5** and **6** as compared to the adducts **3** and **4**, since the bulky methyl groups at 5-position of **1** prevent an attack to give spiro-isoxazolidines **5** and **6**.

The diastereomeric isoxazolidines **3** and **4** were formed via different two-plane orientation complexes. A cycloaddition of the *Z*-nitrone **2** via an *exo* transition state (*exo* arrangement between N-*Ph* and C=O groups) results in the formation of isoxazolidine **3** as the major product. Cycloaddition through the *endo* transition state (N-*Ph* and C=O groups are on opposite sides) give the minor isomer **4**. The ratio of the diastereomers should reflect secondary orbital interactions and repulsive interactions caused by steric hindrance. An examination of both transition states in these terms reveals that secondary orbital interactions are not significant and that repulsions between the phenyl group on nitrogen and the substituents on the dipolarophile **1** are minimized in the *exo* transition state. The ratio of both epimers **3** and **4**, given in Table 1, supports this prediction, as do molecular mechanics calculations. The regio- and stereochemistry of the cycloaddition of nitrones **2** to **1** seems to be controlled by steric effects rather than by frontier orbital interactions.

Experimental Part

Melting points were determined on a Kofler hot plate m.p. apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian VXR 300 (300 MHz) spectrometer (*TMS* as internal standard, $CDCl_3$, δ-values in ppm, *J* in Hz). 3,3-Methylene-5,5-dimethyl-2-pyrrolidinone was prepared by treatment of 2,2,6,6-tetramethyl-4-piperidone monohydrate in chloroform with 50% aqueous NaOH under catalysis of *TEBA* and piperidine [27].

2-Phenyl-3-(X-phenyl)-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro-[4,4]-non-2-enes **3** *and* **4**

N-Phenyl-C-aryl-nitrones **2** (10 mmol) and 3,3-methylene-5,5-dimethyl-2-pyrrolidinone (1.25 g, 10 mmol) in dry toluene (50 ml), were heated under reflux for 5–36 h (TLC). Concentration under reduced pressure and chromatography using chloroform gave corresponding cycloadducts after purification by crystallization from ethanol (see Table 1).

2,3-Diphenyl-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3a**)

^{1}H-NMR: 1.28 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 2.05 (d, $J_{AB} = 14.1$ Hz, 1 H, H_B-9), 2.41 (d, d, $J_{3,4B} = 8.1$ Hz, $J_{AB} = 12.3$ Hz, 1 H, H_B-4), 2.43 (d, 1 H, H_A-9), 3.14 (d, d, $J_{3,4A} = 7.8$ Hz, 1 H, H_A-4),

4.97 (d, d, 1 H, H-3), 6.27 (br. s, 1 H, NH), 6.88–7.50 (m, 10 H, aromat. H). ^{13}C-NMR: 29.88 (q, CH_3), 30.06 (q, CH_3), 47.45 and 47.95 (t, t, C-4, C-9), 53.95 (s, C-8), 69.93 (d, C-3), 84.85 (s, C-5), 116.91, 122.28, 126.74, 127.61, 128.43, 128.85, 141.07, 151.05 (aromat. C), 173.57 (s, C-6).

2,3-Diphenyl-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro-[4,4]-non-2-ene (**4a**)

^{1}H-NMR (*DMSO-d_6*): 1.20 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 2.05 (s, 2 H, H_2-9), 2.62 (d, d, $J_{3,4B}$ = 8.0 Hz, J_{AB} = 13 Hz, 1 H, H_B-4), 2.81 (d, d, $J_{3,4A}$ = 7.2 Hz, 1 H, H_A-4), 4.72 (d, d, 1 H, H-3), 6.81–7.54 (m, 10 H, aromat. H). ^{13}C-NMR (*DMSO-d_6*): 29.48 (q, CH_3), 30.15 (q, CH_3), 47.03 and 48.53 (t, t, C-4, C-9), 52.67 (s, C-8), 68.10 (d, C-3), 85.49 (s, C-5), 114.63, 121.12, 126.82, 127.45, 128.47, 128.65, 141.42, 151.28 (aromat. C), 170.80 (s, C-6).

2-Phenyl-3-(2-chlorophenyl)-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3b**)

^{1}H-NMR: 1.23 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.94 (d, J_{AB} = 14.1 Hz, 1 H, H_B-9), 2.23 (d, d, $J_{3,4B}$ = 6.9 Hz, J_{AB} = 12.0 Hz, 1 H, H_B-4), 2.35 (d, 1 H, H_A-9), 3.35 (d, d, $J_{3,4A}$ = 7.5 Hz, 1 H, H_A-4), 5.36 (d, d, 1 H, H-3), 6.86–7.79 (m, 9 H, aromat. H). ^{13}C-NMR: 29.96 (q, CH_3), 30.15 (q, CH_3), 45.71 and 47.78 (t, t, C-4, C-9), 53.84 (s, C-8), 66.60 (d, C-3), 85.43 (s, C-5), 115.57, 121.98, 127.41, 128.13, 128.56, 128.64, 129.75. 132.43, 139.24, 150.74 (aromat. C), 173.32 (s, C-6).

Some relevant signals corresponding to a minor isomer **4b** were also clearly observed in the crude reaction mixture. ^{1}H-NMR: 1.25 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 2.21 (d, J_{AB} = 13.0 Hz, 1 H, H_B-9), 2.25 (d, 1 H, H_A-9), 2.77 (d, d, $J_{3,4B}$ = 8.0 Hz, J_{AB} = 12 Hz, 1 H, H_B-4), 2.88 (d, d, $J_{3,4A}$ = 8.0 Hz, 1 H, H_A-4), 5.13 (d, d, 1 H, 3-H).

2-Phenyl-3-(4-chlorophenyl)-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3c**)

^{1}H-NMR: 1.27 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 2.00 (d, J_{AB} = 13.8 Hz, 1 H, H_B-9), 2.33 (d, d, $J_{3,4B}$ = 7.8 Hz, J_{AB} = 12.6 Hz, 1 H, H_B-4), 2.40 (d, 1 H, H_A-9), 3.09 (d, d, $J_{3,4A}$ = 7.8 Hz, 1 H, H_A-4), 4.93 (d, d, 1 H, H-3), 5.94 (br. s, 1 H, NH), 6.89–7.42 (m, 9 H, aromat. H). ^{13}C-NMR: 29.98 (q, CH_3), 30.11 (q, CH_3), 47.67 and 47.85 (t, t, C-4, C-9), 53.91 (s, C-8), 69.56 (d, C-3), 84.92 (s, C-5), 116.62, 122.81, 128.27, 128.55, 129.07, 133.53, 139.41, 151.01 (aromat. C), 173.33 (s, C-6).

Signals corresponding to a minor isomer **4c** were also clearly observed in the crude reaction mixture. ^{1}H-NMR: 1.30 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 2.02 (d, J_{AB} = 12.3 Hz, 1 H, H_B-9), 2.33 (d, 1 H, H_A-9), 2.66 (d, d, $J_{3,4B}$ = 7.5 Hz, J_{AB} = 12.0 Hz, 1 H, H_B-4), 2.95 (d, d, $J_{3,4A}$ = 7.5 Hz, 1 H, H_A-4), 4.54 (d, d, 1 H, H-3).

2-Phenyl-3-(2,4-dichlorophenyl)-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro-[4,4]-non-2-ene (**4d**)

^{1}H-NMR: 1.26 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.96 (d, J_{AB} = 13.8 Hz, 1 H, H_B-9), 2.20 (d, d, $J_{3,4B}$ = 8.1 Hz, J_{AB} = 12.6 Hz, 1 H, H_B-4), 2.33 (d, 1 H, H_A-9), 3.34 (d, d, $J_{3,4A}$ = 6.6 Hz, 1 H, H_A-4), 5.33 (d, d, 1 H, H-3), 6.41 (br. s, 1 H, NH), 6.88–7.74 (m, 8 H, aromat. H). ^{13}C-NMR: 30.23 (q, CH_3), 30.43 (q, CH_3), 45.56 and 47.71 (t, t, C-4, C-9), 54.22 (s, C-8), 66.47 (d, C-3), 85.70 (s, C-5), 115.54, 122.39, 128.04, 128.94, 129.34, 129.81, 133.22, 134.06, 138.16, 150.82 (aromat. C), 173.37 (s, C-6).

2-Phenyl-3-(2-fluorophenyl)-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro-[4,4]-non-2-ene (**3e**)

^{1}H-NMR: 1.26 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.97 (d, J_{AB} = 14.1 Hz, 1 H, H_B-9), 2.33 (d, d, $J_{3,4B}$ = 7.2 Hz, J_{AB} = 12.3 Hz, 1 H, H_B-4), 2.36 (d, 1 H, H_A-9), 3.23 (d, d, $J_{3,4A}$ = 6.0 Hz, 1 H, H_A-4), 5.27 (d, d, 1 H, H-3), 6.87 (br. s, 1 H, NH), 6.98–7.69 (m, 9 H, aromat. H). ^{13}C-NMR: 29.36 (q, CH_3), 30.12 (q, CH_3), 45.81 and 47.75 (t, t, C-4, C-9), 53.85 (s, C-8), 63.77 (d, C-3), 85.33 (s, C-5), 116.09, 124.77, 128.58, 129.21, 129.29, 151.15, 158.61, 161.88 (aromat. C), 173.56 (s, C-6).

Signals corresponding to a minor isomer **4e** were clearly observed in the crude reaction mixture. ^{1}H-NMR: 1.25 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.32 (d, J_{AB} = 12.0 Hz, 1H, H_B-9), 2.37 (d, 1H, H_A-9), 2.76 (d, d, $J_{3,4B}$ = 8.0 Hz, J_{AB} = 12.0 Hz, 1H, H_B-4), 2.88 (d, d, $J_{3,4A}$ = 8.0 Hz, 1H, H_A-4), 5.02 (d, d, 1H, H-3).

2-Phenyl-3-(2-nitrophenyl)-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3f**)

^{1}H-NMR: 1.23 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.91 (d, J_{AB} = 13.8 Hz, 1H, H_B-9), 2.24 (d, d, $J_{3,4B}$ = 8.4 Hz, J_{AB} = 12.0 Hz, 1H, H_B-4), 2.27 (d, 1H, H_A-9), 3.48 (d, d, $J_{3,4A}$ = 8.1 Hz, 1H, H_A-4), 5.65 (d, d, 1H, H-3), 6.88–8.11 (m, 9H, aromat. H). ^{13}C-NMR: 30.18 (q, CH_3), 30.43 (q, CH_3), 46.66 and 47.88 (t, t, C-4, C-9), 54.16 (s, C-8), 66.47 (d, C-3), 86.02 (s, C-5), 115.28, 122.29, 125.32, 128.76, 128.94, 129.35, 134.31, 137.71, 148.14, 150.76 (aromat. C), 173.37 (s, C-6).

2-Phenyl-3-(3-nitrophenyl)-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro-[4,4]-non-2-ene (**3g**)

^{1}H-NMR: 1.29 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.04 (d, J_{AB} = 13.8 Hz, 1H, H_B-9), 2.38 (d, d, $J_{3,4B}$ = 7.9 Hz, J_{AB} = 12.3 Hz, 1H, H_B-4), 2.41 (d, 1H, H_A-9), 3.18 (d, d, $J_{3,4A}$ = 7.8 Hz, 1H, H_A-4), 5.12 (d, d, 1H, H-3), 6.20 (br. s, 1H, NH), 6.91–8.37 (m, 9H, aromat. H). ^{13}C-NMR: 29.94 (q, CH_3), 30.07 (q, CH_3), 47.34 and 47.59 (t, t, C-4, C-9), 54.04 (s, C-8), 69.27 (d, C-3), 85.24 (s, C-5), 115.93, 116.48, 121.93, 122.47, 122.80, 123.04, 128.69, 128.74, 129.88, 132.99, 148.98 (aromat. C), 173.21 (s, C-6).

Signals corresponding to a minor isomer **4g** were observed as well in the crude reaction mixture. ^{1}H-NMR: 1.29 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.02 (d, J_{AB} = 14 Hz, 1H, H_B-9), 2.40 (d, 1H, H_A-9), 2.78 (d, d, $J_{3,4B}$ = 7.8 Hz, J_{AB} = 12.0 Hz, 1H, H_B-4), 2.96 (d, d, $J_{3,4A}$ = 7.5 Hz, 1H, H_A-4), 4.75 (d, d, 1H, H-3).

2-Phenyl-3-(4-nitrophenyl)-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro-[4,4]-non-2-ene (**3h**)

^{1}H-NMR: 1.17 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.97 (d, J_{AB} = 14.1 Hz, 1H, H_B-9), 2.11 (d, 1H, H_A-9), 2.35 (d, d, $J_{3,4B}$ = 7.5 Hz, J_{AB} = 12.6 Hz, 1H, H_B-4), 3.06 (d, d, $J_{3,4A}$ = 7.2 Hz, 1H, H_A-4), 5.19 (d, d, 1H, H-3), 6.82–8.27 (m, 9H, aromat. H). ^{13}C-NMR: 29.29 (q, CH_3), 29.85 (q, CH_3), 45.97 and 46.28 (t, t, C-4, C-9), 52.94 (s, C-8), 67.80 (d, C-3), 85.58 (s, C-5), 114.85, 121.38, 123.86, 123.93, 127.80, 128.20, 128.47, 146.81, 149.60, 150.78 (aromat. C), 171.89 (s, C-6).

2-Phenyl-3-(4-methylphenyl)-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3i**)

^{1}H-NMR: 1.26 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.03 (d, J_{AB} = 13.8 Hz, 1H, H_B-9), 2.33 (s, 3H, CH_3), 2.40 (d, d, $J_{3,4B}$ = 8.1 Hz, J_{AB} = 12.3 Hz, 1H, H_B-4), 2.44 (d, 1H, H_A-9), 3.10 (d, d, $J_{3,4A}$ = 7.8 Hz, 1H, H_A-4), 4.90 (d, d, 1H, H-3), 6.87–7.44 (m, 9H, aromat. H). ^{13}C-NMR: 21.12 (q, CH_3), 29.95 (q, CH_3), 30.11 (q, CH_3), 47.87 and 48.24 (t, t, C-4, C-9), 53.93 (s, C-8), 69.89 (d, C-3), 84.88 (s, C-5), 115.84, 116.55, 122.33, 126.78, 127.20, 128.41, 129.56, 137.30, 138.11, 151.16 (aromat. C), 173.74 (s, C-6).

Signals of a minor isomer **4i** were also observed in the crude reaction mixture. ^{1}H-NMR: 1.25 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.02 (d, J_{AB} = 13.0 Hz, 1H, H_B-9), 2.42 (d, 1H, H_A-9), 2.62 (d, d, $J_{3,4B}$ = 7.5 Hz, J_{AB} = 12.0 Hz, 1H, H_B-4), 2.98 (d, d, $J_{3,4A}$ = 8.0 Hz, 1H, H_A-4), 4.50 (d, d, 1H, H-3).

2-Phenyl-3-(4-methoxyphenyl)-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3j**)

^{1}H-NMR: 1.28 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.05 (d, J_{AB} = 13.5 Hz, 1H, H_B-9), 2.38 (d, d, $J_{3,4B}$ = 8.0 Hz, J_{AB} = 12.0 Hz, 1H, H_B-4), 2.45 (d, 1H, H_A-9), 3.10 (d, d, $J_{3,4A}$ = 8.0 Hz, 1H, H_A-4), 3.81 (s, 3H, OCH_3), 4.88 (d, d, 1H, H-3), 6.42 (br. s, 1H, NH), 6.88–7.41 (m, 9H, aromat. H). ^{13}C-

NMR: 29.87 (q, CH_3), 30.06 (q, CH_3), 47.67 and 48.06 (t, t, C-4, C-9), 53.94 (s, C-8), 55.28 (q, OCH_3), 69.71 (d, C-3), 84.78 (s, C-5), 114.21, 116.59, 122.44, 127.99, 128.39, 132.71, 150.97, 159.09 (aromat. C), 173.71 (s, C-6).

2-Phenyl-3-(4-methoxyphenyl)-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**4j**)

^{1}H-NMR: 1.30 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.03 (d, J_{AB} = 15.3 Hz, 1H, H_B-9), 2.33 (d, J_{AB} = 13.0 Hz, 1H, H_A-9), 2.61 (d, d, $J_{3,4B}$ = 8.3 Hz, 1H, H_B-4), 2.99 (d, d, $J_{3,4A}$ = 8.0 Hz, 1H, H_A-4), 3.80 (s, 3H, OCH_3), 4.47 (d, d, 1H, H-3), 5.84 (br. s, 1H, NH), 6.87–7.49 (m, 9H, aromat. H). ^{13}C-NMR: 30.12 (q, CH_3), 30.35 (q, CH_3), 48.28 and 49.10 (t, t, C-4, C-9), 53.42 (s, C-8), 55.32 (q, OCH_3), 69.34 (d, C-3), 84.21 (s, C-5), 114.33, 116.17, 116.80, 122.06, 128.40, 128.57, 151.04, 159.21 (aromat. C), 173.01 (s, C-6).

2-Phenyl-3-(2-furyl)-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3k**)

Yield: 25%, m.p. 221–223°C. $C_{18}H_{20}N_2O_3$ (312.36). ^{1}H-NMR: 1.30 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.09 (d, J_{AB} = 13.8 Hz, 1H, H_B-9), 2.47 (d, 1H, H_A-9), 2.64 (d, d, $J_{3,4B}$ = 7.5 Hz, J_{AB} = 12.3 Hz, 1H, H_B-4), 3.04 (d, d, J_{AB} = 7.2 Hz, 1H, H_A-4), 4.96 (d, 1H, H-3), 6.30–7.40 (m, 8H, aromat. and furan H). ^{13}C-NMR: 30.00 (q, CH_3), 30.10 (q, CH_3), 43.24 and 47.97 (t, t, C-4, C-9), 53.94 (s, C-8), 64.57 (d, C-3), 85.09 (s, C-5), 108.05, 110.51, 117.11, 123.09, 128.46, 142.47, 152.65 (aromat. and furan C), 173.47 (s, C-6). Relevant signals corresponding to a minor isomer **4k** were also clearly observed in the crude reaction mixture. ^{1}H-NMR: 1.28 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.97 (d, J_{AB} = 14.0 Hz, 1H, H_B-9), 2.35 (d, 1H, H_A-9), 2.64 (d, d, $J_{3,4B}$ = 8.0 Hz, J_{AB} = 12.0 Hz, 1H, H_B-4), 3.18 (d, d, $J_{3,4A}$ = 7.8 Hz, 1H, H_A-4), 4.79 (d, d, 1H, H-3). The ratio of **3k** : **4k** was 79 : 21.

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