The reaction of α- and ω-methylenelactams with nitrones. Influence of electronic and geometric factors on the stereoselectivity of their 1,3-dipolar cycloaddition

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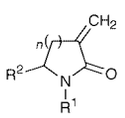
Various four to six-membered ring α- and ω-methylenelactams **1**–**5** were reacted with nitrones **6** and afforded good yields of spiroadducts **7**–**12** through a regiospecific [3 + 2] cycloaddition. Owing to the creation of at least two new asymmetric centres, mixtures of diastereoisomers were usually obtained whose structures were established by two-dimensional NOESY experiments or X-ray crystallography. Among the dipolarophiles, 3-methyleneazetidin-2-ones **1** yielded adducts with a very high stereoselectivity. A similar behaviour was also observed with α-benzoylnitrone **6a** as a 1,3-dipole. Electronic and geometric interactions of the reagents **1**–**5** and **6** in the course of the cycloaddition process were discussed in order to account for the experimental stereochemical outcomes.

Introduction

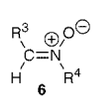
Heterocyclic spirocompounds are of synthetic interest in organic chemistry. Indeed, the presence of a spirocarbon atom induces a relative steric strain and allows the possible thermal or acid/base promoted rearrangement of these products, yielding new and often unexpected heterocycles.[1–7] Some spirocompounds and their rearrangement products have recently shown interesting applications in botany and agronomics.[1,2,8] The cycloaddition between dipolarophiles bearing an exocyclic carbon–carbon double bond and appropriate 1,3-dipoles is one of the best methods for the synthesis of bicyclic spirocompounds. We have recently reported the reaction of 3-methyleneisoindolones (methylenephthalimidines) with nitrones.[9] Other examples of 1,3-dipolar cycloadditions between lactams bearing an *exo* or *endo* cyclic conjugated double bond have been described.[10–15] In the course of our research, two papers dealing with the reaction of α-ethylidenelactams with 1,3-dipoles have been published.[16,17] Strauss and Otto reacted α-ethylideneazetidin-2-ones with the single *N*-methyl-α-phenylnitrone and obtained very unstable adducts under drastic conditions in modest yields.[17] We report here our results for the 1,3-dipolar cycloaddition of several α- and ω-methylene lactams **1**–**5** (Table 1) with nitrones **6a**–**e** (Table 2), yielding spirocycloadducts **7**–**12**. Important differences of diastereoselectivity were encountered in this general reaction, which are discussed according to the nature of the starting materials and the interactions during the transition state. Some accounts are also given concerning a comparative reactivity of methylenelactams.

Table 1 α-Methylenelactams prepared



	n	R^1	R^2
1a	0	*p*-MeO-Ar-	–H
1b	0	*p*-Me-Ar-	–H
1c	0	*p*-O_2N-Ar-	–H
2a	1	$–CH_3$	–H
2b	1	$–CH_3$	Ph
3a	2	$–CH_3$	–H
3b	2	Ph-CH_2–	–H

Table 2 Nitrones **6** prepared



6

	R^3	R^4
a	PhCO–	Ph–
b	Ph–	Ph–
c	Ph–	$PhCH_2$–
d	Ph–	Bu^t
e	Ph–	Me–

Results and discussion

The [3 + 2] cycloaddition of α-methylenelactams **1**–**3** and nitrones **6** gave high yields of stable spiroadducts **7**,**8a**–**p** (Schemes 1–3, Table 3). The bislactam **4** afforded bisadducts **9**–**10** upon reaction with **6a** (Scheme 4); cycloaddition of **4** with diphenylnitrone **6b** furnished an inextricable mixture of adducts that we were unable to separate and this reaction was not further investigated. The 5-methylenepyrrolidin-2-one **5** was very unstable[18] and reacted only with the highly reactive benzoylnitrone **6a** (Scheme 5). All methylenelactams **1**–**5** reacted completely and no secondary product was detected, as shown either by ^{1}H NMR analysis of the crude reaction mixtures or TLC.

Regiochemistry

All cycloadditions afforded a single regioisomer, identified as a 5,5-disubstituted isoxazolidine. This regiospecificity was established by ^{1}H and ^{13}C NMR spectroscopy. First, the ^{13}C chemical shift of the spiro centre of all adducts was between 80 and 100 ppm (see Experimental section); this value located the spiro centre near the very electronegative oxygen atom of the isoxazolidine ring. Secondly, the identification in all adducts of an ABX system by ^{1}H NMR was in accordance with the 5-substituted isoxazolidine structure only. These results supported literature reports.[19,20] The theoretical calculations,

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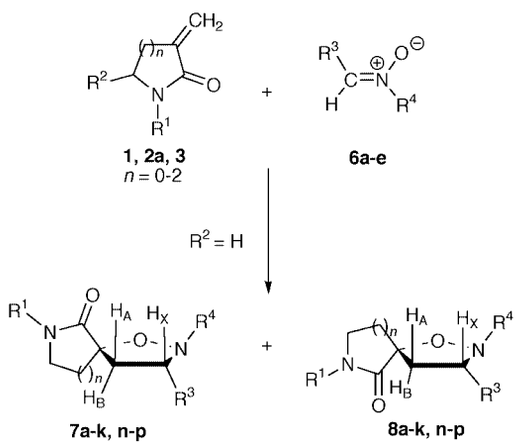
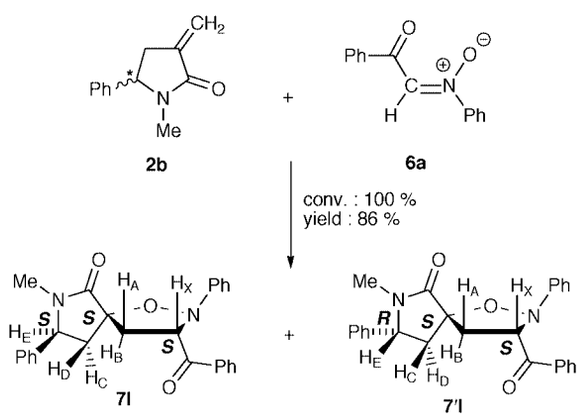
Table 3 Reaction of α-methylenelactams with nitrones; reaction conditions, yields and selectivity

Entry	Methylene-lactam	Nitrone	Adducts	*T*/°C[a]	Time/h	Yield (%)	Isomers ratio (%)[b]
1	**1a**	**6a**	**7a**	110	0.25	92[c]	100:0
2	**1a**	**6b**	**7b**:**8b**	110	0.5	83[c]	>95:<5
3	**1a**	**6d**	**7c**	110	6	65[c]	100:0
4	**1a**	**6e**	**7d**:**8d**	55[e]	240	62[c]	>90:<10
5	**1b**	**6b**	**7e**:**8e**	110	1	78[c]	>95:<5
6	**1b**	**6c**	**7f**:**8f**	110	3	81	90:10
7	**1c**	**6a**	**7g**	110	0.25	92[c]	100:0
8	**1c**	**6c**	**7h**:**8h**	110	3	94[c]	[d]
9	**1c**	**6d**	**7i**	110	6	84[c]	100:0
10	**2a**	**6a**	**7j**	80	0.5	72[c]	100:0
11	**2a**	**6b**	**7k**:**8k**	50	96	67	85:15
12	**2b**	**6a**	**7l**:**7′l**	110	1	86	70:30
13	**2b**	**6b**	**7m**:**7′m**:**8m**:**8′m**	110	6	88	54:31:9:6
14	**3a**	**6a**	**7n**	80	0.5	80[c]	100:0
15	**3a**	**6b**	**7o**:**8o**	50	96	73	80:20
16	**3b**	**6a**	**7p**	20[f]	2.5	90[c]	100:0

[a] Reaction in toluene unless indicated otherwise. [b] Evaluated by ^{1}H NMR in the crude mixture. [c] Yield of pure **7**. [d] Not evaluated by ^{1}H NMR. [e] Reaction at 110 °C caused some formation of by-products. [f] Ethyl acetate.



Scheme 1

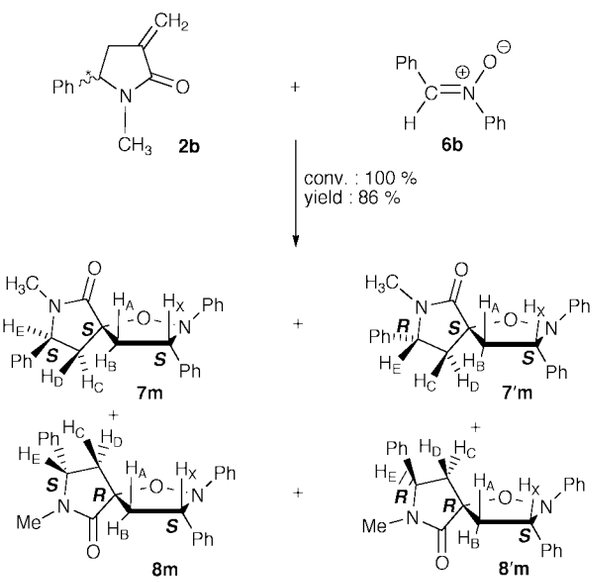


Scheme 2

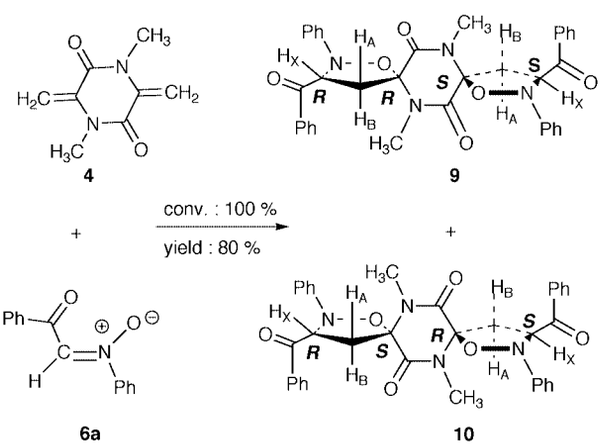
performed by the semi-empirical PM3 method included in CS Chem3D Pro. did not provide any useful information and were frequently in contradiction with our experimental results. A strong interaction between the electrophilic sp^2 carbon (=*C*H$_2$) of α-methylenelactams **1**–**3** and the 'soft' carbon of the dipolar linkage was supposed to explain to a great extent the specificity of the orientation.

Stereochemistry

The cycloaddition of *non-substituted* α-methylenelactams **1**–**3** or 5-methylenepyrrolidin-2-one **5** with nitrones **6** led to cyclo-

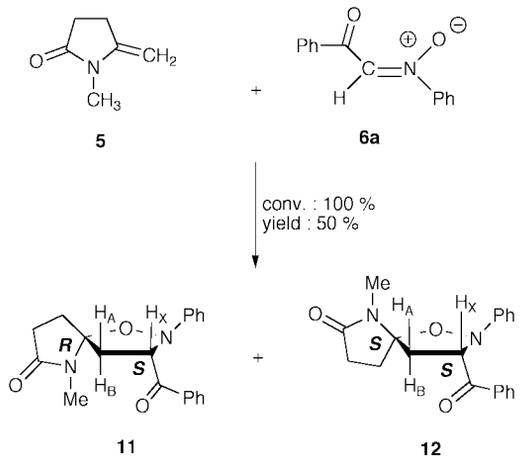


Scheme 3



Scheme 4

adducts having two *new* chiral centres, *i.e.* the quaternary spiro atom and the carbon bearing the R^3 substituent of the isoxazolidine ring; four asymmetric carbons were created in the case of bislactam **4**. The percentage of stereoisomers in the crude reaction mixtures has been evaluated by ^{1}H NMR



5 6a 11 12

Scheme 5

spectroscopy from the relative integration of the N–CH_X proton of the isoxazolidine ring (relative accuracy ±5%) or was achieved only after careful separation of the different adducts by flash chromatography. Exact structures of spirolactams **7**–**12** were established by two-dimensional NMR spectroscopy (NOESY experiments) and X-ray crystallography. The formation of diastereoisomeric adducts was never caused by any interconversion between the *Z*/*E* nitrones,[21,22] the relative configuration (*Z*) of the dipole was always preserved in the spirocompounds.

Once the structures of cycloadducts were established and in order to explain the observed stereochemistry, we investigated the electronic and steric factors between reagents **1**–**5** and **6** during their cycloadditions.

Cycloaddition of α-methylenelactams 1–3

The terms 'endo' and 'exo' refer to the position of the α-methylenelactam carbonyl group relative to the dipolar linkage during the transition state.

Non-substituted α-methylenelactams (R^2 = H, Scheme 1) should normally afford four diastereoisomers distributed into two pairs of enantiomers **7** and **8**.

All cycloadditions involving α-benzoylnitrone **6a** (Table 3, entries 1, 7, 10, 14, 16) were stereospecific; the lactam ring size had no influence on stereospecificity. As a representative experiment,[23] the configuration of the single product from the reaction of the substituted azetidinone **1a** with **6a** was established by X-ray crystallography: the benzoyl function (R^3) and the lactam carbonyl group were in an *anti* configuration (Fig. 1). The structure **7a** (*rel*-4*R*,7*S*) was consequently assigned to this adduct. As shown in Fig. 2, the *endo* approach which would lead to the stereoisomers **8** was strongly disadvantaged, since the two carbonyl groups should be very close together, an improbable circumstance because of their natural electronic repulsion.

The cycloaddition of α-methylenelactams with nitrones **6b**–**e** processed with stereoselectivity. Although minor diastereoisomers were difficult to obtain in a pure form, we have isolated spiroazetidinones **7f** and **8f** (R^4 = Bn) for exact characterisation purposes. Their structures were elucidated from two-dimensional ^{1}H–^{1}H NOESY spectra and NOE effects reported in Table 4. The structure **8f** *rel*-(4*R*,7*R*) was unambiguously assigned to the minor isomers by the presence of a very strong NOE effect between the H_X proton and those of the β-lactam ring. Such an interaction was absent in the case of **7f** *rel*-(4*R*,7*S*). The semi-empirical PM3 method and Dreiding™ models procured correct representations of spirolactams **7f** and **8f** and both these structures provided confirmation of the results of the two-dimensional NMR spectroscopy. These results were unambiguously generalised to other adducts.

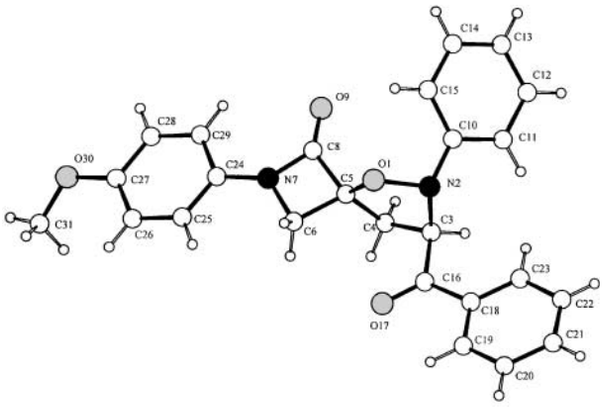


Fig. 1 ORTEP view of adduct **7a** (arbitrary numbering).

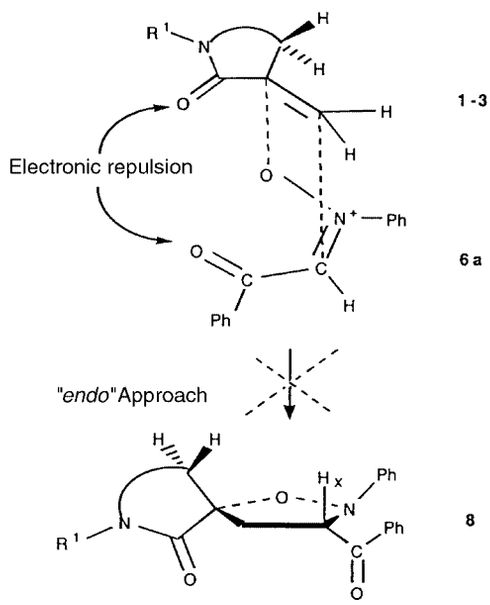


Fig. 2 The forbidden interaction between α-methylenelactams and α-benzoylnitrone.

Indeed, the formation of **7** was facilitated by the absence of any steric hindrance in the *exo* approach of reagents, and thus the formation of **8** was all the more unfavourable, as the bulk of the R^4 group of nitrones **6** increased and interacted with the intracyclic methylenic hydrogens (CH_2-C=CH_2) of lactams **1**–**3** (Fig. 3 and Table 3, entries 2–6). Indeed, stereospecificity was reached with *N*-*tert*-butylnitrone **6d** (Table 3, entries 3 and 9).

We noticed that greater amounts of the minor adducts **8** were obtained with five and six-membered rings lactams **2** and **3**. Indeed, whereas methyleneazetidin-2-ones **1** remained entirely rigid during the nitrone approach, pyrrolidinones and piperidinones could adopt a conformation (half envelope for **2**, *pseudo* chair for **3**) which minimised the steric effect of the methylene protons. The *endo* approach was consequently less unfavourable.

Upon reaction with nitrones, the *5-substituted* methylenelactam **2b**, which already carried an asymmetric centre, would normally give rise to eight diastereoisomers, distinguished in Scheme 3 as four diastereoisomeric pairs of enantiomers **7**:**7′**:**8**:**8′**. However, α-benzoylnitrone **6a** afforded only two diastereoisomeric pairs **7l** *rel*-(3*R*,5*R*,8*R*) and **7′l** *rel*-(3*R*,5*S*, 8*S*), resulting respectively from the *anti* (major) and *syn* (minor) approaches of the nitrone in relation to the hindering 5-phenyl substituent (Scheme 2). As shown in Fig. 2, the repulsive interaction of both carbonyl groups during the approach of reagents forbade the formation of **8**.

Table 4 Two-dimensional ^{1}H NMR (NOESY experiments, 300 MHz) for adducts **7f**, **8f**[a]

	7f	H_X	H_A	H_B	H_L	CH_2	**8f**	H_X	H_A	H_B	H_L	CH_2
	H_X	/	+	+	−	(+)	H_X	/	+	+	+	(+)
	H_A	+	/	+	−	−	H_A	+	/	+	−	−
	H_B	+	+	/	−	−	H_B	+	+	/	−	−
	H_L	−	−	−	/	−	H_L	+	−	−	/	(+)
	CH_2	(+)	−	−	−	/	CH_2	(+)	−	−	(+)	/

[a] H_L = β-lactam protons; CH_2 = benzylic protons; "+" = strong NOE effect; "(+)" = weak NOE effect; "−" = no effect; the grey tint square indicates the determining ^{1}H–^{1}H-correlation through space for adduct **8**.

Table 5 Two-dimensional ^{1}H NMR (NOESY experiments, 300 MHz) for adducts **7m**, **7′m** and **8m**[a]

7m	H_X	H_A	H_B	H_C	H_D	H_E	**7′m**	H_X	H_A	H_B	H_C	H_D	H_E	**8m**	H_X	H_A	H_B	H_C	H_D	H_E
H_X	/	+	+	−	−	−	H_X	/	+	+	−	−	−	H_X	/	+	+	−	−	−
H_A	+	/	+	−	−	−	H_A	+	/	+	−	−	−	H_A	+	/	+	+	−	−
H_B	+	+	/	−	+	−	H_B	+	+	/	+	−	−	H_B	+	+	/	−	−	−
H_C	−	−	−	/	+	+	H_C	−	−	+	/	+	+	H_C	−	+	−	/	+	+
H_D	−	−	+	+	/	+	H_D	−	−	−	+	/	+	H_D	−	−	−	+	/	+
H_E	−	−	−	+	+	/	H_E	−	−	−	+	+	/	H_E	−	−	−	+	+	/

[a] "+" = positive NOE effect; "−" = no effect; the grey tint square indicates the determining ^{1}H–^{1}H-correlation through space for each structure.

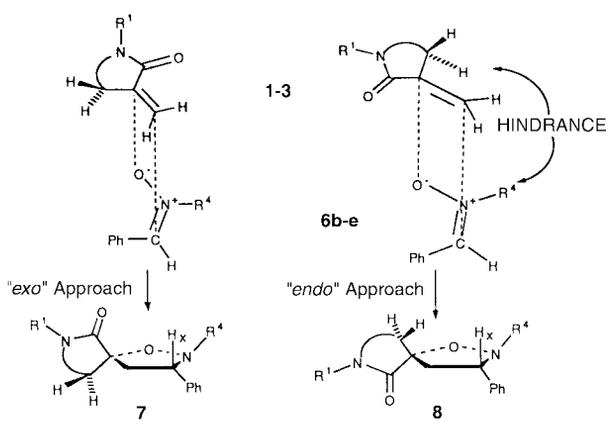


Fig. 3 Interaction of α-methylenelactams and α-phenylnitrones.

The structures of the diastereoisomers (four enantiomeric pairs **7m**:**7′m**:**8m**:**8′m**) stemming from the reaction of diphenylnitrone **2b** with **6b** (Scheme 3) were established from two-dimensional ^{1}H–^{1}H spectroscopy (NOESY experiments) and the NOE effects are summarised in Table 5. Most of the signals of the 2D spectrum of the very minor isomer **8′m** were unfortunately unclear and we could not give satisfactory analysis. The major isomers **7m** *rel*-(3*R*,5*R*,8*R*) and **7′m** *rel*-(3*R*,5*S*,8*S*) were formed (>80%) according to the favoured interaction of the reagents (Fig. 3, *exo* approach); the selectivity proceeding from the *anti* approach towards the 5-phenyl played a secondary part only.

Cycloaddition of 5-methylenepyrrolidin-2-one 5 (Scheme 5)

This ω-methylenelactam gave rise to the non-separable 2,6-diazaspiro[4.4]nonanes **11** (*RS*,*SR*) and **12** (*RR*,*SS*). The 2D NMR NOESY spectrum of the mixture indicated a strong NOE effect between the H_X proton and the N–Me group of the minor isomers exclusively. Consequently, structure **12** has been ascribed to the minor isomer from its representation by CS Chem3D Pro. (PM3). Furthermore, the schematisation of the approach leading to **12** clearly showed that this one was disadvantaged, because it introduced some hindrance between the *N*-phenyl group of **6a** and the *N*-methyl of **5** (Fig. 4). No electronic feature was denoted here, since the position of the lactam carbonyl group never interacted with the carbonyl of the nitrone benzoyl function.

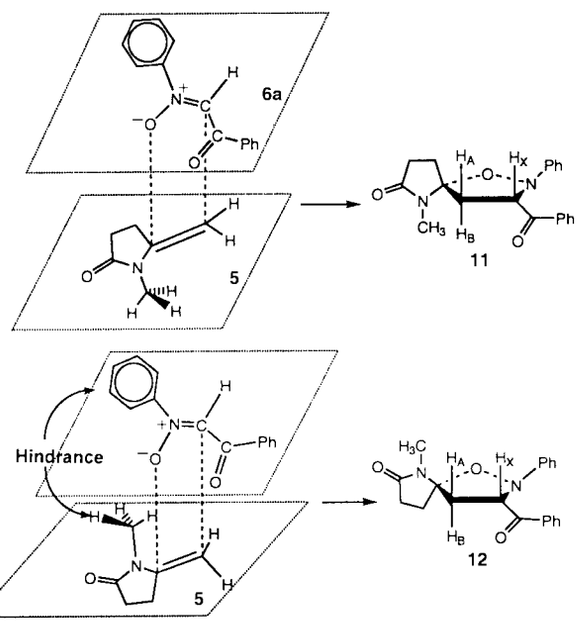


Fig. 4 Interactions of methylenepyrrolidin-2-one **5** and benzoylnitrone **6**.

Cycloadditions of bislactam 4

With **6a**, this molecule gave two pairs of symmetrical adducts **9** and **10** among all those possible. The structure of the major diastereoisomer (80%) was established by X-ray crystallography (Fig. 5); the benzoyl group of each isoxazolidine ring and the neighbouring lactam carbonyl were opposite and this stereochemistry was in accordance with structure **9** *rel*-(3*R*,5*R*,8*S*,11*S*). The very strong electronic repulsion between the C=O groups of **4** and **6a** should normally prevent the formation of **10**. In fact, as shown in Fig. 6, the carbonyl group and the exocyclic methylene group of **4** were not in the same plane. Consequently, the repulsion between the carbonyl groups of **4** and **6a** during the disadvantaged approach leading to **10** was reduced.

Reactivity of methylenelactams

Apart from the stable crystalline 3-methyleneazetidin-2-ones **1**, all other methylenelactams were intrinsically or thermally

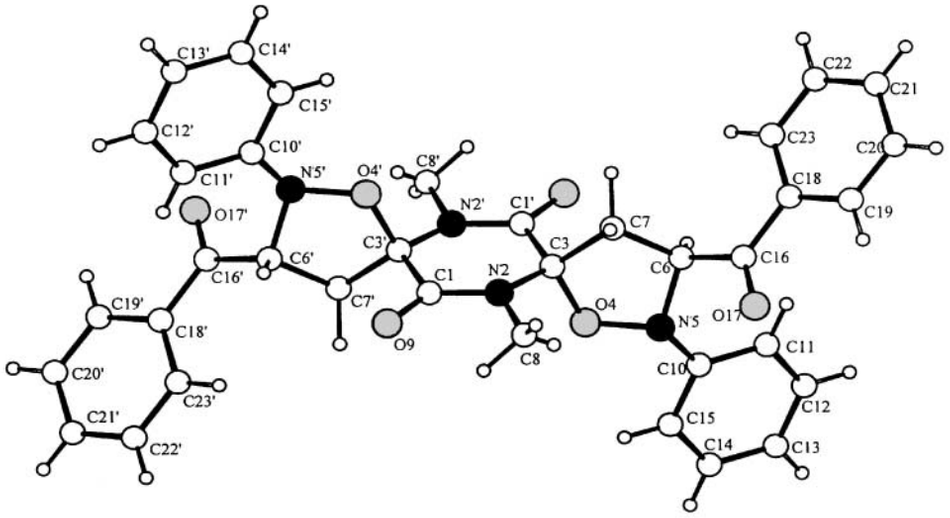


Fig. 5 ORTEP view of bisadduct **9** (arbitrary numbering).

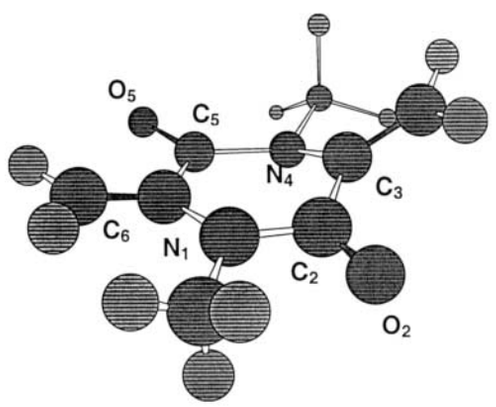


Fig. 6 View of compound **4** modelled by PM3.

fragile and, as shown in Table 3 and Schemes 1–5, we were unable to apply any standard conditions within the scope of their cycloaddition with nitrones. We have recently shown[9] that differential thermal analysis (DTA) proved to be a very useful technique for exploring the thermal behaviour of organic reagents and quickly establishing reaction conditions. DTA was applied here and conditions stated in Table 3 were regarded as ideal. Although any comprehensive comparison of the reactivity of methylenelactams was impossible, some unambiguous conclusions were drawn from our results.

In particular, all thermal analyses of equimolecular mixtures of 3-methyleneazetidin-2-ones **1** and nitrones **6** revealed that the reagents exothermically cycloadded immediately they melted. The very high reactivity of β-lactams **1** was also immediately obvious from the experimental results (Table 3, entries 1–9). There was no doubt that the release of the strong intracyclic strain in the course of the cycloaddition explained the very good dipolarophilic activity of **1**. Conversely, piperidin-2-one **3b** and 5-methylenepyrrolidin-2-one **5** were not strained rings and their relative reactivity was compared using similar reaction conditions. When the ω-methylenelactam **5** was reacted with nitrone **6b** (20 °C, 30 h), the dipole was quantitatively recovered, whereas **5** degraded into a gummy polymer. In the same reaction conditions, the α-methylenelactam **3b** gave 35% of spiroadducts, and cycloaddition was complete within a few days. The presence of a conjugated withdrawing group is a well-known factor enhancing the dipolarophilic character of an alkene.[24] The weak reactivity of the unactivated 5-methylenepyrrolidin-2-one **5** was compared with methylenephthalimidines, their benzo derivatives, whose more stable character permitted stronger reaction conditions.[9]

The bislactam **4** did not add two equivalents of nitrone **6a** simultaneously: the reaction of **4** with only one equivalent of α-benzoylnitrone gave approximately equivalent amounts of monoadducts and bisadducts **9** and **10** (see Experimental section). The formation of these latter compounds was rather slow, probably for steric reasons. Piperazine **4** might be considered as an α- and ω-methylenelactam, because the exocyclic double bonds were located in the α-position of both the carbonyl group and nitrogen: the lone pair of each nitrogen atom compensated for the electronic deficiency of this exocyclic double bond. The reactivity of the latter was halfway between those of α- and ω-methylenelactams.

Conclusions

The [3 + 2] cycloaddition of α-methylenelactams **1**–**3** with nitrones **6** was a general and high-yielding regiospecific reaction. Its stereoselectivity was discussed from the possible electronic or steric interactions of reagents during their approaches. The major stereoisomers **7** were the result of the preferential approach locating the lactam carbonyl group in the *exo* position relative to the dipolar linkage. The *endo* approach was entirely forbidden when α-benzoylnitrone **6a** was used as a dipole because of electronic repulsion between the carbonyl groups of both reagents. It was also greatly prevented in the case of other nitrones, whose nitrogen substituent R^4 created a steric hindrance towards the lactam hydrogen atoms. Particularly, the rigidity and strong internal strain of 3-methyleneazetidin-2-ones **1** explained their exceptionally high reactivity and the great stereoselectivity of their cycloadditions with nitrones. These properties should be investigated because of the importance of the β-lactam ring and possible later chemical transformations of spirocompounds. The bislactam **4** behaved as an α- and ω-methylenelactam and gave simple exploitable results with α-benzoylnitrone **6a** only. The ω-methylenelactam **5** was much less reactive, because of its own unstable character and the deactivation of the *exo*-methylene group: it reacted only with **6a**. The formation of the major stereoisomers **11** was explained by the absence of steric hindrance between the N–R^4 group of the nitrone and the N–Me moiety of **5**.

Experimental

General

Melting points were taken using a Dr Tottoli apparatus and are uncorrected. IR spectra were measured on a Bruker Spectrospin (FT-IR) IFS-45 apparatus. ^{1}H and ^{13}C NMR spectra were run on a Bruker Spectrospin AC200 spectrometer at 200.13

MHz (^{1}H) and 50.32 MHz (^{13}C). Two-dimensional ^{1}H–^{1}H spectroscopy (NOESY experiments) of compounds **7f**, **8f**, **7m**, **7′m**, **8m** and **8′m** were obtained from a Bruker Avance 300 spectrometer at 300.13 MHz. All compounds were dissolved in $CDCl_3$ (except for **11** and **12**) with 0.1% TMS as internal reference. The ^{13}C NMR spectra were obtained from proton-noise decoupled spectra. Chemical shifts are in ppm on the δ scale and coupling constants J are given in Hz. In ^{13}C NMR spectra, carbons are numbered according to the IUPAC nomenclature rules for spirocompounds. Spectroscopic data of very minor diastereoisomers are acquired from the crude mixtures of adducts and only well-resolved signals are reported here. Differential thermal analysis was performed using a Mettler Thermal Mechanical Analyser TMA 40. Samples of 15.0 mg of reagents **1**–**6** or equimolar mixtures of **1**:**6** were placed in an aluminium crucible and their thermal behaviour automatically analysed (20–150 °C; temperature gradient: +10 °C min^{-1}). All flash liquid chromatographies were performed in 2.5 cm inside diameter Pyrex columns with Kieselgel 60, particle size of 0.063–0.200 mm, from Merck (art. 1.07734.1000). Diethyl ether and THF (Carlo Erba, 99.5% min) were allowed to stand over anhydrous calcium chloride for 24 hours and thoroughly dried on sodium wire before use; toluene was directly dried over sodium wire. Other reagents or solvents were commercial products and used as received. *Owing to the strong electrophilic character of most α-methylenelactams, great care should be taken during their manipulation and protective gloves should be worn*.

Preparation of starting materials

The α-benzoyl-*N*-phenylnitrone **6a** [*N*-(2-phenyl-2-oxoethylidene)aniline *N*-oxide] was prepared by the following modified method.[25] A solution of commercial nitrosobenzene (5.35 g, 0.05 mol) in acetone (40 cm^3) was cooled with an ice–salt bath. Phenacylpyridinium bromide (13.9 g, 0.05 mol) was dissolved in the minimum of water (20–30 cm^3) and cooled. The two resultant suspensions were combined and 1 mol dm^{-3} aqueous sodium hydroxide solution was *very slowly* added *with continuous pH control* over a period of *ca*. 3–4 h at 0 °C under vigorous stirring. The addition was stopped when the pH reached and remained at 7 (40–50 ml were required). After 1 h in the cold bath, the orange–yellow solid was filtered, washed with ice water, then with diethyl ether and air-dried. Yield: 9.8 g (87%). Mp: 107–109 °C. *Addition of the sodium hydroxide solution without extreme care led to an intractable gum*.

Nitrones **6b**–**d** were obtained by the hydrogen peroxide oxidation of the corresponding *N*-substituted benzylamines in 85–90% yields.[26] The *N*-methyl-α-phenylnitrone **6e** [(*N*-benzylidene)methylamine *N*-oxide] was synthesised from benzaldehyde and methylhydroxylamine hydrochloride in 86% yield.[27]

The 3-methyleneazetidin-2-ones **1a**–**c** were obtained on a 20–30 g scale from the readily accessible 2-bromomethyl-3-bromopropanoic acid.[28,29]

The lactams **2a**, **3a** and **4** were prepared from *N*-methylpyrrolidin-2-one, *N*-methylpiperidin-2-one and 1,4-dimethylpiperazine-2,5-dione ("sarcosine anhydride") respectively, following substantially modified known procedures.[30,31] Sodium hydride (60% dispersion in mineral oil, 8.2 g, 205 mmol) and diethyl oxalate (43.2 cm^3, 49 g, 315 mmol) were suspended in anhydrous diethyl ether or THF (150 cm^3) and the mixture heated at 35–40 °C under an argon atmosphere. The appropriate lactam (150 mmol) was added dropwise (or portionwise for the solid piperazinedione) over a one hour period. Stirring was continued for 3 days at 35–40 °C, and the mixture cooled to 0 °C. The grey pasty solid was filtered off, washed with anhydrous diethyl ether and dried under reduced pressure (40 °C, 20 mmHg). This sodium salt of the 3-ethoxalyllactam and paraformaldehyde (9.5 g, 315 mmol) were then suspended in xylene (200 cm^3) and the heterogeneous mixture was stirred at 100 °C for 90 minutes. After cooling to room temperature, the solid residues were filtered through a pad of Celite®. The filtrate was dried over anhydrous sodium sulfate and most of the xylene evaporated under reduced pressure. The resulting oil (**2a**, **3a**) was purified by vacuum distillation and stored at −20 °C. The bismethylenelactam **4** was recrystallised from a propan-1-ol–cyclohexane mixture.

1-Methyl-3-methylenepyrrolidin-2-one 2a. 60%, $bp_{0.2\ mmHg}$: 48–49 °C, n_D^{20}: 1.5025. δ_H: 2.80 (m, 2H), 2.98 (s, 3H, CH_3), 3.43 (m, 2H), 5.32 (t, 1H, *J* 2.2), 5.96 (t, 1H, *J* 2.2).

1-Methyl-3-methylenepiperidin-2-one 3a. 45%, $bp_{0.2\ mmHg}$: 55–58 °C, n_D^{20}: 1.5080. δ_H: 1.89 (m, 2H), 2.56 (dd, 2H, *J* 1.5 and 6.0), 3.01 (s, 3H, CH_3), 3.39 (m, 2H), 5.25 (dd, 1H, *J* 1.5 and 3.5), 6.16 (dd, 1H, *J* 1.5 and 3.5).

1,4-Dimethyl-3,6-dimethylenepiperazine-2,5-dione 4. 55%, mp: 140–142 °C (rapid heating, decomp.). δ_H: 3.30 (s, 6H, N-*Me*), 4.99 (m, 2H), 5.88 (m, 2H).

The 5-substituted pyrrolidin-2-one **2b** was synthesised from ethyl bromomethylacrylate[32] and *N*-methylbenzylideneimine, following the well-described procedure of Villiéras *et al*.[33,34]

1-Methyl-3-methylene-5-phenylpyrrolidin-2-one 2b. 65%, mp: 68–70 °C. ν_{max} (KBr)/cm^{-1}: 1685 (C=O), 1660 (C=C). δ_H: 2.62 (ddt, 1H, *J* 2.5, 4.4 and 17.0), 2.69 (s, 3H, N-C*H*$_3$), 3.22 (ddt, 1H, *J* 2.5, 8.5 and 17.0), 4.50 (dd, 1H, *J* 4.4 and 8.5), 5.35 (dd, 1H, *J* 2.3 and 2.7), 6.07 (dd, 1H, *J* 2.3 and 2.7), 7.2–7.4 (m, 5H).

The piperidin-2-one **3b** was obtained by the Ac_2O promoted rearrangement of *N*-benzylnipecotic acid (*N*-benzyl-3-carboxypiperidine).[35] The authors used an excessive amount of acetic anhydride. Dividing this quantity by 10 gave high yields of **3b** and greatly simplified the work-up of the crude mixture; the methylenepiperidin-2-one was thus obtained in a 75% overall yield from the commercial inexpensive ethyl nipecotate.

The 5-methylenepyrrolidin-2-one **5** was prepared by the following modified procedure.[18] Aqueous 40% methylamine (3 ml, 35 mmol) was slowly added at 0 °C to pent-3-eno-4-lactone (α-angelicalactone) (3.5 g, 35 mmol). After 2 hours in the cold, water was distilled off (20 °C, 10 mmHg), leaving an oil which was crystallised from diethyl ether. The crude product (3 g, 23 mmol) was dehydrated at 70–80 °C under high vacuum (0.15 mmHg) and **5** was collected in liquid nitrogen. Overall yield: 56%, mp: 58–59 °C. This lactam was used immediately; it polymerised readily even at low temperature.

General procedure for the preparation of substituted 1-oxo-5-oxa-2,6-diazaspiro[3.4]octanes 7,8a–i (Table 3, entries 1–9)

The equimolecular mixture of 3-methyleneazetidin-2-one **1** and nitrone **6** (2.5 mmol) in anhydrous toluene (5 cm^3) was stirred at 55–110 °C under an argon atmosphere until reaction was complete (TLC, cyclohexane–ethyl acetate, 80:20). The solvent was then evaporated under reduced pressure and the adducts isolated by addition of 95% ethanol (3 cm^3), cooling at −10 °C, filtration, washing with ethanol (5 cm^3) and air-drying. Recrystallisation from propan-1-ol gave analytically pure products **7**.

7-Benzoyl-2-(4-methoxyphenyl)-1-oxo-5-oxa-2,6-diazaspiro-[3.4]octane 7a. Yield: 92%, mp: 155–156 °C. δ_H: 2.75 (dd, 1H$_B$, *J* 6.6 and 12.8), 3.08 (d, 1H$_A$, *J* 12.8), 3.78 (s, 3H, O-C*H*$_3$), 3.85 (d, 1H, *J* 6.5), 4.10 (d, 1H, *J* 6.5), 5.38 (d, 1H$_X$, *J* 6.6), 6.9–8.1 (m, 14H). δ_C: 34.0 (C^8), 55.3 (O-*C*H$_3$), 55.5 (C^3), 69.3 (C^7), 91.3 (C^4), 114.3–156.3 (aromatic C), 164.0 (C^1), 195.4 (*C*=O, benzoyl). ν_{max}(KBr)/cm^{-1}: 1740 (C=O β-lactam), 1690 (C=O benzoyl) (Found: C, 72.3; H, 5.5; N, 6.9. $C_{25}H_{22}N_2O_4$ requires C, 72.45; H, 5.35; N, 6.76%).

The total structure has been published.[23]

6,7-Diphenyl-2-(4-methoxyphenyl)-1-oxo-5-oxa-2,6-diazaspiro[3.4]octane 7b:8b. Yield 83%. *Major diastereoisomer* **7b**: mp: 130–131 °C. δ_H: 2.71 (dd, $1H_B$, *J* 3.8 and 12.8), 3.13 (dd, $1H_A$, *J* 7.1 and 12.8), 3.75 (d, 1H, *J* 6.1), 3.78 (s, 3H, O-CH_3), 3.80 (d, 1H, *J* 6.1), 4.89 (dd, $1H_X$, *J* 3.8 and 7.1), 6.8–7.4 (m, 14H). δ_C: 42.2 (C^8), 55.3 (O-CH_3), 55.3 (C^3), 70.5 (C^7), 89.3 (C^4), 112.6–151.5 (aromatic C), 164.1 (C^1). ν_{max}(KBr)/cm^{-1}: 1745 (Found: C, 74.2; H, 5.8; N, 7.3. $C_{24}H_{22}N_2O_3$ requires C, 74.59; H, 5.74; N, 7.25%). *Minor diastereoisomer* **8b**: selected δ_H: 4.71 (t, $1H_X$, *J* 7.8); selected δ_C: 44.8 (C^8), 54.9 (C^3), 69.1 (C^7), 89.3 (C^4).

2-(4-Methoxyphenyl)-1-oxo-7-phenyl-6-*tert*-butyl-5-oxa-2,6-diazaspiro[3.4]octane 7c. Yield: 65%, mp: 155–156 °C. δ_H: 1.12 (s, 9H, C(CH_3)$_3$), 2.61 (dd, $1H_B$, *J* 6.7 and 12.7), 3.07 (dd, $1H_A$, *J* 7.9 and 12.7), 3.60 (d, 1H, *J* 5.9), 3.78 (s, 3H, O-CH_3), 3.80 (d, 1H, *J* 5.9), 4.52 (dd, $1H_X$, *J* 6.7 and 7.9), 6.8–7.5 (m, 9 H). δ_C: 26.3 (3 CH_3), 46.2 (C^8), 55.5 (O-CH_3), 55.5 (C^3), 59.7 (C(CH_3)$_3$), 62.7 (C^7), 88.2 (C^4), 116.5–142.6 (aromatic C), 164.7 (C^1). ν_{max}(KBr)/cm^{-1}: 1745 (Found: C, 72.1; H, 7.1; N, 7.6. $C_{22}H_{26}N_2O_3$ requires C, 72.11; H, 7.15; N, 7.64%).

2-(4-Methoxyphenyl)-6-methyl-1-oxo-7-phenyl-5-oxa-2,6-diazaspiro[3.4]octane 7d. The equimolecular mixture of **1a** and **6e** (2.5 mmol) in toluene (5 cm^3) was stirred at 50–60 °C under argon for 10 days. Cyclohexane (5 cm^3) was then added, giving a white solid. After filtration and air-drying, **7d** was recrystallised from cyclohexane–ethyl acetate (1:1). Yield: 62%, mp: 125–126 °C. δ_H: 2.65 (dd, $1H_B$, *J* 6.5 and 12.5), 3.07 (dd, $1H_A$, *J* 7.2 and 12.5), 3.54 (d, 1H, *J* 5.9), 3.73 (s, 3H, O-CH_3), 3.84 (d, 1H, *J* 5.9), 3.92 (dd, $1H_X$, *J* 6.5 and 7.2), 6.8–7.4 (m, 9H). δ_C: 42.8 (N-CH_3), 43.2 (C^8), 54.5 (O-CH_3), 54.5 (C^3), 71.6 (C^7), 87.7 (C^4), 113.4–155.5 (aromatic C), 163.7 (C^1). ν_{max}(KBr)/cm^{-1}: 1750 (Found: C, 70.5; H, 6.3; N, 8.6. $C_{19}H_{20}N_2O_3$ requires C, 70.35; H, 6.21; N, 8.64%).

6,7-Diphenyl-2-(4-methylphenyl)-1-oxo-5-oxa-2,6-diazaspiro-[3.4]octane 7e:8e. Total yield: 78%. *Major diastereoisomer* **7e**: mp: 131–132 °C. δ_H: 2.30 (s, 3H, CH_3), 2.69 (dd, $1H_B$, *J* 5.8 and 12.6), 3.22 (dd, $1H_A$, *J* 7.2 and 12.6), 3.49 (d, 1H, *J* 6.1), 3.76 (d, 1H, *J* 6.1), 4.90 (dd, $1H_X$, *J* 5.8 and 7.2), 7.0–7.6 (m, 14H). NOESY experiment for adduct **7e** is reported in Table 4. δ_C: 20.8 (CH_3), 42.4 (C^8), 55.2 (C^3), 70.6 (C^7), 89.3 (C^4), 116.7–150.9 (aromatic C), 164.5 (C^1). ν_{max}(KBr)/cm^{-1}: 1760 (Found: C, 77.5; H, 6.0; N, 7.7. $C_{24}H_{22}N_2O_2$ requires C, 77.81; H, 5.99; N, 7.56%). *Minor diastereoisomer* **8e**: selected δ_H: 3.70 (d, 1H), 3.95 (d, 1H), 4.72 (t, $1H_X$, *J* 7.6); selected δ_C: 44.9 (C^8), 54.8 (C^3), 69.2 (C^7), 89.3 (C^4).

6-Benzyl-2-(4-methylphenyl)-1-oxo-7-phenyl-5-oxa-2,6-diazaspiro[3.4]octane 7f:8f. For identification purpose, the crude mixture was dissolved in hot toluene (2 cm^3) and chromatographed on silica gel (150 g) with cyclohexane–ethyl acetate (85:15) as eluent. Total yield: 81%. *Major diastereoisomer* **7f**: mp: 117–118 °C. δ_H: 2.30 (s, 3H, CH_3), 2.70 (dd, $1H_B$, *J* 7.3 and 12.9), 3.20 (dd, $1H_A$, *J* 7.3 and 12.9), 3.65 (d, 1H, *J* 5.9), 3.80 (d, 1H, *J* 5.9), 4.01 (d, 1H, *J* 14.0), 4.11 (d, 1H, *J* 14.0), 4.28 (t, $1H_X$, *J* 7.3), 7.1–7.5 (m, 14H). δ_C: 20.8 (CH_3), 43.5 (C^8), 54.8 (C^3), 61.3 (CH_2-Ph), 69.8 (C^7), 89.0 (C^4), 116.7–139.3 (aromatic C), 165.3 (C^1). ν_{max}(KBr)/cm^{-1}: 1740 (Found: C, 78.0; H, 6.3; N, 7.4. $C_{25}H_{24}N_2O_2$ requires C, 78.10; H, 6.29; N, 7.29%). *Minor diastereoisomer* **8f**: mp: 177–178 °C. δ_H: 2.24 (s, 3H, CH_3), 2.82 (dd, $1H_B$, *J* 7.2 and 13.1), 2.92 (dd, $1H_A$, *J* 7.2 and 13.1), 3.70 (d, 1H, *J* 6.2), 3.75 (d, 1H, *J* 6.2), 3.90 (d, 1H, *J* 13.6), 4.00 (d, 1H, *J* 13.6), 4.03 (t, $1H_X$, *J* 7.2), 7.0–7.4 (m, 14H). δ_C: 21.1 (CH_3), 48.5 (C^8), 54.5 (C^3), 59.2 (CH_2-Ph), 69.3 (C^7), 89.0 (C^4), 116.0–139.0 (aromatic C), 165.5 (C^1). NOESY experiments for **7f** and **8f** are summarised in Table 4.

7-Benzoyl-2-(4-nitrophenyl)-1-oxo-6-phenyl-5-oxa-2,6-diazaspiro[3.4]octane 7g. Yield: 92%, mp: 187–189 °C. δ_H: 2.80 (dd, $1H_B$, *J* 6.6 and 12.8), 3.20 (d, $1H_A$, *J* 12.8), 3.95 (d, 1H, *J* 7.1), 4.30 (d, 1H, *J* 7.1), 5.47 (d, $1H_X$, *J* 6.6), 7.3–8.3 (m, 14H). δ_C: 34.2 (C^8), 55.9 (C^3), 69.7 (C^7), 92.0 (C^4), 115.8–149.5 (aromatic C), 165.9 (C^1), 195.3 (C=O, benzoyl). ν_{max}(KBr)/cm^{-1}: 1740 (C=O β-lactam), 1685 (C=O benzoyl) (Found: C, 66.9; H, 4.5; N, 9.8. $C_{24}H_{19}N_3O_5$ requires C, 67.13; H, 4.46; N, 9.79%).

6-Benzyl-2-(4-nitrophenyl)-1-oxo-7-phenyl-5-oxa-2,6-diazaspiro[3.4]octane 7h:8h. Yield: 94%. *Major diastereoisomer* **7h**: mp: 174–175 °C. δ_H: 2.80 (dd, $1H_B$, *J* 7.2 and 12.9), 3.20 (dd, $1H_A$, *J* 7.2 and 12.9), 3.80 (d, 1H, *J* 6.5), 3.95 (d, 1H, *J* 6.5), 4.02 (d, 1H, *J* 14.0), 4.09 (d, 1H, *J* 14.0), 4.32 (t, $1H_X$, *J* 7.2), 7.3–8.2 (m, 14H). δ_C: 43.5 (C^8), 55.2 (C^3), 61.1 (CH_2-Ph), 69.7 (C^7), 89.4 (C^4), 116.5–143.5 (aromatic C), 166.3 (C^1). ν_{max}(KBr)/cm^{-1}: 1755 (Found: C, 69.5; H, 5.2; N, 10.1. $C_{24}H_{21}N_3O_4$ requires C, 69.39; H, 5.10; N, 10.11%). *Minor diastereoisomer* **8h**: selected δ_C: 44.8 (C^8), 54.8 (C^3), 69.2 (C^7), 89.5 (C^4).

2-(4-Nitrophenyl)-1-oxo-7-phenyl-6-*tert*-butyl-5-oxa-2,6-diazaspiro[3.4]octane 7i. Yield: 84%, mp: 205 °C. δ_H: 1.13 (s, 9H, C(CH_3)$_3$), 2.65 (dd, $1H_B$, *J* 6.6 and 12.8), 3.10 (dd, $1H_A$, *J* 7.8 and 12.8), 3.70 (d, 1H, *J* 6.3), 3.95 (d, 1H, *J* 6.3), 4.54 (dd, $1H_X$, *J* 6.6 and 7.8), 7.2–8.2 (m, 9H). δ_C: 26.1 (3 CH_3), 46.3 (C^8), 55.5 (C^3), 59.7 (C(CH_3)$_3$), 62.6 (C^7), 88.6 (C^4), 116.6–143.4 (aromatic C), 166.2 (C^1). ν_{max}(KBr)/cm^{-1}: 1745 (Found: C, 65.9; H, 6.0; N, 11.0. $C_{21}H_{23}N_3O_4$ requires C, 66.13; H, 6.08; N, 11.02%).

General procedure for the preparation of substituted 1-oxo-6-oxa-2,7-diazaspiro[4.4]nonanes 7,8j–k and 1-oxo-7-oxa-2,8-diazaspiro[4.5]decanes 7,8n–o (Table 3, entries 10, 11, 14, 15)

The mixture of nitrone **6a** or **6b** (5 mmol) and 3-methylene-pyrrolidin-2-one **2a** or piperidin-2-one **3a** (5–7 mmol, see below), was dissolved in dry toluene (5 cm^3) and hydroquinone was added (10–15 mg). The reaction vessel was heated at the appropriate temperature under argon until TLC (ethyl acetate–cyclohexane 70:30) indicated complete consumption of the nitrone. The solvent was evaporated under reduced pressure and the crude residue analysed. The adducts were purified by recrystallisation from *n*-propanol.

8-Benzoyl-2-methyl-1-oxo-7-phenyl-6-oxa-2,7-diazaspiro-[4.4]nonane 7j. Reaction at 80 °C for 30 min with 5 mmol of **2a**. Yield: 72%, mp: 119–121 °C. δ_H: 2.27 (dd, 1H, *J* 7.4 and 8.3), 2.51 (m, 1H, *J* 2.4 and 7.4), 2.62 (dd, $1H_B$, *J* 5.7 and 12.2), 2.91 (s, 3H, N-CH_3), 3.09 (dd, $1H_A$, *J* 8.3 and 12.2), 3.25 (m, 1H, *J* 2.4 and 8.3), 3.55 (m, 1H, *J* 2.4 and 7.4), 5.39 (dd, $1H_X$, *J* 5.7 and 8.3), 7.0–8.1 (m, 10H). δ_C: 30.3 (CH_3), 31.5 (C^4), 40.3 (C^9), 45.9 (C^3), 70.2 (C^8), 84.7 (C^5), 114.5–149.8 (aromatic C), 171.2 (C^1), 196.1 (C=O, benzoyl). ν_{max}(KBr)/cm^{-1}: 1710 (C=O γ-lactam), 1690 (C=O benzoyl) (Found: C, 71.1; H, 5.8; N, 8.3. $C_{20}H_{20}N_2O_3$ requires C, 71.41; H, 5.99; N, 8.33%).

7,8-Diphenyl-2-methyl-1-oxo-6-oxa-2,7-diazaspiro[4.4]-nonane 7k:8k. Reaction at 50 °C for 96 hours with 7.5 mmol of **2a**. Total yield: 67%. *Major diastereoisomer* **7k** (59%): mp: 127 °C. δ_H: 2.12 (m, 1H, *J* 7.3 and 13.8), 2.43 (dd, $1H_B$, *J* 7.6 and 12.3), 2.52 (dd, 1H, *J* 3.2 and 13.8), 2.91 (s, 3H, N-CH_3), 3.12 (dd, $1H_A$, *J* 7.6 and 12.3), 3.24 (dd, 1H, *J* 3.2 and 8.9), 3.54 (dd, 1H, *J* 3.2 and 7.3), 4.91 (t, $1H_X$, *J* 7.6), 6.9–7.6 (m, 10H). δ_C: 30.2 (CH_3), 31.7 (C^4), 45.8 (C^3), 47.2 (C^9), 70.3 (C^8), 83.8 (C^5), 115.0–150.5 (aromatic C), 171.7 (C^1). ν_{max}(KBr)/cm^{-1}: 1700 (Found: C, 74.2; H, 6.6; N, 9.1. $C_{19}H_{20}N_2O_2$ requires C, 74.00; H, 6.54; N, 9.11%). *Minor diastereoisomer* **8k**: selected δ_H: 2.96 (s, 3H, N-CH_3), 4.62 (dd, $1H_X$, *J* 7.8 and 9.7); selected δ_C: 30.3 (CH_3), 45.4 (C^3), 47.8 (C^9), 69.7 (C^8).

9-Benzoyl-2-methyl-1-oxo-8-phenyl-7-oxa-2,8-diazaspiro-[4.5]decane 7n. Reaction at 80 °C for 30 min with 5 mmol of **3a**. Yield: 80%, mp: 136–138 °C. δ_H: 1.90 (m, 2H), 2.32 (dd, $1H_B$,

J 8.4 and 12.0), 2.33 (m, 2H), 2.90 (s, 3H, N-CH_3), 3.35 (m, 2H), 3.41 (dd, 1H$_A$, *J* 8.4 and 12.0), 5.44 (t, 1H$_X$, *J* 8.4), 6.9–8.1 (m, 10H). δ_C: 19.5 (C^4), 32.6 (*C*H$_3$), 35.0 (C^5), 43.7 (C^9), 49.6 (C^3), 71.3 (C^8), 81.0 (C^6), 112.8–151.5 (aromatic C), 168.4 (C^1), 196.4 (*C*=O, benzoyl). ν_{max}(KBr)/cm^{-1}: 1655 (C=O δ-lactam), 1685 (C=O benzoyl) (Found: C, 71.7; H, 6.4; N, 7.8. $C_{20}H_{20}N_2O_3$ requires C, 71.98; H, 6.33; N, 7.99%).

8,9-Diphenyl-2-methyl-1-oxo-7-oxa-2,8-diazaspiro[4.5]decane 7o:8o. Reaction at 50 °C for 96 hours with 7.5 mmol of **3a**. Yield: 73%. *Major diastereoisomer* **7o** (63%), mp: 143 °C. δ_H: 1.89 (m, 2H), 2.18 (dd, 1H$_B$, *J* 9.5 and 12.2), 2.45 (m, 2H), 2.92 (s, 3H, N-CH_3), 3.32 (dd, 1H$_A$, *J* 7.5 and 12.2), 3.38 (m, 2H), 4.95 (dd, 1H$_X$, *J* 7.5 and 9.5), 6.9–7.5 (m, 10H). δ_C: 19.7 (C^4), 33.6 (*C*H$_3$), 34.9 (C^5), 49.7 (C^3), 50.3 (C^9), 70.9 (C^8), 80.5 (C^6), 112.5–154.2 (aromatic C), 169.0 (C^1). ν_{max}(KBr)/cm^{-1}: 1650 (Found: C, 74.4; H, 7.0; N, 8.7. $C_{20}H_{22}N_2O_2$ requires C, 74.51; H, 6.88; N, 8.69%). *Minor diastereoisomer* **8o**: selected δ_H: 3.01 (s, 3H, CH_3), 4.54 (dd, 1H$_X$, *J* 7.3 and 9.9). δ_C: 19.5 (C^4), 32.8 (*C*H$_3$), 35.4 (C^5), 47.1 (C^3), 48.8 (C^9), 69.3 (C^8), 81.7 (C^6), 169.0 (C^1).

Reaction of 1-benzyl-3-methylenepiperidin-2-one 3b with α-benzoylnitrone 6a (Table 3, entry 16)

The equimolecular mixture of **3b** and **6a** (5 mmol) was dissolved in ethyl acetate (5 cm^3); hydroquinone (10 mg) was then added and the solution was stirred for 2.5 hours. The solvent was evaporated and the residue purified by chromatography on silica gel (eluent: cyclohexane–ethyl acetate, 70:30), giving **7p** as a very viscous oil which crystallised at or below −10 °C. Yield: 90%. δ_H: 1.68–2.33 (m, 4H), 2.31 (dd, 1H$_B$, *J* 8.3 and 11.9), 3.20 (m, 2H), 3.36 (dd, 1H$_A$, *J* 8.3 and 11.9), 4.15 (d, 1H, *J* 14.5), 4.71 (d, 1H, *J* 14.5), 5.48 (t, 1H$_X$, *J* 8.3), 6.9–8.2 (m, 15H). δ_C: 19.7 (C$_4$), 32.7 (C$_5$), 43.8 (*C*H$_2$, benzyl), 46.9 (C$_3$), 50.4 (C^{10}), 71.4 (C^9), 81.5 (C^6), 113.2–149.9 (aromatic C), 178.5 (C^1), 196.8 (*C*=O, benzoyl). ν_{max}(KBr)/cm^{-1}: 1690 (C=O benzoyl), 1660 (C=O lactam) (Found: C, 76.2; H, 6.2; N, 6.8. $C_{27}H_{26}N_2O_3$ requires C, 76.03; H, 6.14; N, 6.57%).

Reaction of 1-methyl-3-methylene-5-phenylpyrrolidin-2-one 2b with nitrones 6a–b (Table 3, entries 12, 13)

An equimolecular mixture of methylenelactam **2b** and nitrone **6** (2.5 mmol) was stirred in boiling toluene (5 cm^3) during the appropriate reaction time. After evaporation of the solvent, the residue was purified by column chromatography on silica gel.

8-Benzoyl-3,7-diphenyl-2-methyl-1-oxo-6-oxa-2,7-diazaspiro-[4.4]nonane 7l:7′l. The crude residue was dissolved in DMF (2 cm^3) and chromatographed on 120 g of silica gel (eluent: cyclohexane–ethyl acetate 70:30). Total yield: 86%. *Major diastereoisomer* **7l**: 60%; mp: 167–169 °C. δ_H: 2.05 (dd, 1H$_D$, *J* 7.1 and 14.4), 2.65 (dd, 1H$_B$, *J* 5.6 and 12.3), 2.70 (s, 3H, CH_3), 3.00 (dd, 1H$_C$, *J* 7.1 and 14.4), 3.20 (dd, 1H$_A$, *J* 8.2 and 12.3), 4.70 (t, 1H$_E$, *J* 7.1), 5.45 (dd, 1H$_X$, *J* 5.6 and 8.2), 7.0–8.1 (m, 15H). δ_C: 28.6 (*C*H$_3$), 40.0 (C^9), 42.4 (C^4), 61.4 (C^3), 70.3 (C^8), 84.6 (C^5), 116.0–149.6 (aromatic C), 195.7 (*C*=O benzoyl). *Minor diastereoisomer* **7′l**: 26%, mp: 148–149 °C. δ_H: 2.50 (dd, 1H$_D$, *J* 3.9 and 14.4), 2.70 (dd, 1H$_B$, *J* 5.5 and 12.2), 2.75 (s, 3H, CH_3), 2.80 (dd, 1H$_C$, *J* 8.3 and 14.4), 3.12 (dd, 1H$_B$, *J* 8.2 and 12.2), 4.43 (dd, 1H$_E$, *J* 3.9 and 8.3), 5.45 (dd, 1H$_X$, *J* 5.5 and 8.2), 7.0–8.1 (m, 15H). δ_C: 28.6 (*C*H$_3$), 40.6 (C^9), 41.0 (C^4), 60.9 (C^3), 69.8 (C^8), 84.6 (C^5), 115.8–150.6 (aromatic C), 195.7 (*C*=O benzoyl). ν_{max}(KBr)/cm^{-1}: 1710 (C=O γ-lactam), 1690 (C=O benzoyl) (Found: C, 75.4; H, 5.6; N, 6.8. $C_{26}H_{24}N_2O_3$ requires C, 75.71; H, 5.86; N, 6.79%).

2-Methyl-1-oxo-3,7,8-triphenyl-6-oxa-2,7-diazaspiro[4.4]-nonane 7m:7′m:8m:8′m. The crude reaction mixture was dissolved in toluene (2 cm^3) and chromatographed on 120 g of silica gel (eluent: cyclohexane–ethyl acetate 85:15, then 70:30). Total yield: 88%. *Diastereoisomer* **7m**: 48%; mp: 150 °C. δ_H: 1.98 (dd, 1H$_D$, *J* 7.1 and 14.2), 2.40 (dd, 1H$_B$, *J* 7.7 and 12.4), 2.72 (s, 3H, CH_3), 2.95 (dd, 1H$_C$, *J* 7.1 and 14.2), 3.28 (dd, 1H$_A$, *J* 7.7 and 12.4), 4.71 (t, 1H$_E$, *J* 7.1), 4.95 (t, 1H$_X$, *J* 7.7), 6.9–7.5 (m, 15H). δ_C: 29.1 (*C*H$_3$), 41.6 (C^4), 47.8 (C^9), 62.1 (C^3), 71.1 (C^8), 84.3 (C^5), 117.2–151.0 (aromatic C), 173.0 (C=O). *Diastereoisomer* **7′m**: 27%, mp: 143 °C. δ_H: 2.27 (dd, 1H$_D$, *J* 4.8 and 13.9), 2.55 (dd, 1H$_C$, *J* 8.0 and 13.9), 2.71 (dd, 1H$_B$, *J* 7.2 and 12.2), 2.80 (s, 3H, CH_3), 2.98 (dd, 1H$_A$, *J* 10.0 and 12.2), 4.44 (dd, 1H$_E$, *J* 4.8 and 8.0), 4.60 (dd, 1H$_X$, *J* 7.2 and 10.0), 6.7–7.6 (m, 15H). δ_C: 29.5 (*C*H$_3$), 42.2 (C^9), 49.2 (C^4), 61.4 (C^3), 70.3 (C^8), 84.5 (C^5), 115.5–152.0 (aromatic C), 171.9 (C=O). *Diastereoisomer* **8m**: 8%, mp: 137–138 °C. δ_H: 1.88 (dd, 1H$_B$, *J* 6.9 and 13.9), 2.55 (dd, 1H$_D$, *J* 7.4 and 12.2), 2.70 (dd, 1H$_A$, *J* 6.9 and 13.9), 2.71 (s, 3H, CH_3), 3.00 (dd, 1H$_C$, *J* 9.7 and 12.2), 4.46 (dd, 1H$_E$, *J* 7.4 and 9.7), 4.60 (t, 1H$_X$, *J* 6.9), 6.8–7.5 (m, 15H); selected δ_C: 28.6 (*C*H$_3$), 41.8 (C^4), 48.2 (C^9), 62.3 (C^3), 71.0 (C^8), 84.1 (C^5), 172.8 (C=O). *Diastereoisomer* **8′m**: 5%, mp: 209 °C. δ_H: 1.95 (dd, 1H$_D$, *J* 7.6 and 14.0), 2.28 (dd, 1H$_C$, *J* 8.0 and 14.0), 2.45 (dd, 1H$_B$, *J* 6.0 and 13.1), 2.51 (s, 3H, CH_3), 2.65 (dd, 1H$_A$, *J* 10.0 and 13.1), 4.52 (dd, 1H$_E$, *J* 7.6 and 8.0), 4.90 (dd, 1H$_X$, *J* 6.0 and 10.0), 6.4–7.4 (m, 15H). ν_{max}(KBr)/cm^{-1}: 1700 (Found: C, 78.2; H, 6.4; N, 7.3. $C_{25}H_{24}N_2O_2$ requires C, 78.10; H, 6.29; N, 7.29%). All NOESY experiments for the latter adducts are summarised in Table 5.

Cycloaddition of the substituted piperazine-2,5-dione 4 with α-benzoyl-*N*-phenylnitrone 6a: preparation of 3,11-dibenzoyl-6,13-dimethyl-7,14-dioxo-2,10-diphenyl-1,9-dioxa-2,6,10,13-tetra-azadispiro[4.2.4.2]tetradecane 9:10 (Scheme 4)

A solution of the bislactam **4** (420 mg, 2.53 mmol) and nitrone **6a** (1.14 g, 5.06 mmol) in toluene (5 cm^3) was stirred at 80 °C for 4 hours, the reaction being monitored by TLC (ethyl acetate–cyclohexane, 20:80). The mixture assumed an orange–red colour and a solid formed within 15 minutes. When TLC indicated complete conversion of reagents, the solvent was evaporated under reduced pressure, giving a red gum which was stirred with 95% ethanol for several hours until precipitation of adducts was complete. Filtration and washing with ethanol gave a mixture of the two bisadducts **9**:**10**. Fractional crystallisation from propan-1-ol gave pure **9**; it was unfortunately impossible to isolate the second diastereoisomer **10** by column chromatography, owing to its total insolubility in common solvents. Total yield: 80%. *Major diastereoisomer* **9**: 46%; mp: 205–206 °C. δ_H: 3.07 (dd, 1H$_B$, *J* 10.1 and 13.3), 3.35 (s, 3H, CH_3), 3.41 (dd, 1H$_A$, *J* 7.3 and 13.3), 5.53 (dd, 1H$_X$, *J* 7.3 and 10.1), 7.0–8.0 (m, 20H). δ_C: 29.5 (*C*H$_3$), 43.9 (C^4), 71.4 (C^3), 90.8 (C^5), 119.2–148.6 (aromatic C), 165.1 (*C*=O), 194.3 (*C*=O benzoyl). *Minor diastereoisomer* **10**: selected δ_H: 3.24 (s, 3H, CH_3), 3.60 (m, 1H), 5.61 (m, 1H$_X$). ν_{max}(KBr)/cm^{-1}: 1670 (Found: C, 69.8; H, 5.3; N, 8.8. $C_{36}H_{32}N_4O_6$ requires C, 70.12; H, 5.23; N, 9.09%).

Evidence of the formation of monoadducts: A solution of the bislactam **4** (165 mg, 1.0 mmol) and nitrone **6a** (225 mg, 1.0 mmol) in toluene (5 cm^3) was stirred at 80 °C for 1 hour, until TLC (cyclohexane–ethyl acetate, 80:20) indicated complete reaction of the dipole. The solvent was evaporated under reduced pressure (20 °C) and the crude red residue analysed by ^{1}H NMR spectroscopy. The relative molar proportions of unreacted bislactam **4** (40%), monoadducts (30%) and bisadducts (30%) were determined with an average accuracy of 5% from the signals at 5.4–5.6 ppm (H$_X$ protons of mono and bisadducts) and 5.8–5.9 ppm (unshielded methylenic protons of **4** and monoadducts; these latter signals, located at 4.91 and 5.81 ppm, and the ones of bislactam **4**—4.99 and 5.88 ppm—were sufficiently separated to allow a correct estimation).

Crystallographic study of bis-adduct **9**:† A colourless monocrystal with dimensions 0.240 × 0.120 × 0.060 mm was obtained by slow evaporation of a solution of **9** in 95% ethanol and mounted on an Enraf Nonius CAD4 diffractometer. Radiation used: graphite filtered Cu-Kα, $\lambda = 1.54180$ Å; $\mu = 0.745$. Data were collected at 293 ± 2 °C. All scanning used the $\theta/2\theta$ technique with $4.74° < \theta < 67.89°$. The structure was solved by direct methods using SHELXL93.[36a] Atomic scattering factors were taken from International Tables of X-Ray Crystallography.[37] Crystallographic data of **9**: $C_{36}H_{32}N_4O_6$, $M = 616.66$ g mol^{-1}, $d_{calc} = 1.326$ g cm^{-3}, triclinic system, *P*-1 space group, $a = 8.932(2)$, $b = 9.670(3)$, $c = 10.105(30)$ Å, $\alpha = 100.95(2)°$, $\beta = 105.61(2)°$, $\gamma = 106.37(2)°$, $V = 772.4(3)$ Å^3, $Z = 1$. Number of independent reflections: 2797 (R(int) = 0.0327); they were 2080 reflections with $I > 2\sigma(I)$. The refinement[36b] converged to $R_1(F) = 0.050$, $wR_2 = 0.1087$ with $R_1 = \Sigma$ (Fobs − Fcalc)/Σ (Fobs). Residual electron density between −0.216 and 0.189 e Å^{-3}.

Reaction of 1-methyl-5-methylenepyrrolidin-2-one 5 with nitrone 6a (Scheme 5)

Freshly prepared 1-methyl-5-methylenepyrrolidin-2-one **5** (2.5 mmol), α-benzoylnitrone **6a** (2.5 mmol) and hydroquinone (15 mg) were stirred under argon at room temperature in ethyl acetate (5 cm^3) for 30 hours. TLC ($CHCl_3$) showed complete reaction of **6a**. After evaporation of the solvent (25 °C, 15 mmHg), the oily residue was analysed by ^{1}H NMR spectroscopy and 2D NOESY experiments. The adducts were not separable but their admixture was crystallised from 95% ethanol (3 cm^3) and washed with the same solvent (5 cm^3).

3-Benzoyl-7-oxo-2-phenyl-1-oxa-2,6-diazaspiro[4.4]nonane 11:12. Yield: 50%; *Major diastereoisomer* **11**: δ_H (C_6D_6): 1.17 (m, 1H), 1.83 (m, 3H), 2.25 (m, 1H), 2.66 (dd, 1H, *J* 7.5 and 13.3), 2.93 (s, 3H, CH_3), 4.62 (dd, 1H$_X$, *J* 7.5 and 8.6), 6.8–8.4 (m, 10H). δ_C: 28.7 (C^9), 32.4 (C^8), 40.5 (C^4), 69.1 (C^3), 100.2 (C^5), 114.9–149.5 (aromatic C), 174.9 (*C*=O, lactam), 195.8 (*C*=O, benzoyl). *Minor diastereoisomer* **12**: δ_H (C_6D_6): 1.17 (m, 1H), 1.95 (m, 2H), 2.25 (m, 3H), 2.41 (s, 3H, CH_3), 4.65 (m, 1H$_X$), 6.8–8.4 (m, 10H). δ_C: 25.5 (C^9), 32.9 (C^8), 39.8 (C^4), 69.1 (C^3), 100.2 (C^5), 114.9–149.5 (aromatic C), 174.9 (*C*=O, lactam), 195.6 (*C*=O, benzoyl). ν_{max} (KBr)/cm^{-1}: 1720 (C=O lactam), 1690 (C=O benzoyl) (Found: C, 71.5; H, 6.0; N, 8.2. $C_{20}H_{20}N_2O_3$ requires C, 71.41; H, 5.99; N, 8.33%).

Attempted reaction of 1-methyl-5-methylenepyrrolidin-2-one 5 with nitrone 6b

Freshly distilled 1-methyl-5-methylenepyrrolidin-2-one **5** (3 mmol), α,*N*-diphenylnitrone **6b** (2.5 mmol) and hydroquinone (15 mg) were stirred at room temperature in ethyl acetate (5 cm^3) for 30 hours under an argon atmosphere. A reddish oily residue was obtained after evaporation of the solvent (30 °C, 15 mmHg). Its ^{1}H NMR analysis showed complete disappearance of **5** and the absence of any H$_X$ proton corresponding to the expected spiroadduct. Addition of 95% ethanol (5 cm^3) and cooling to −10 °C for several hours gave a white solid, mp: 114–115 °C, which had characteristics identical to **6b** (90% recovery).

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References

1 K. C. Liu and R. K. Howe, *J. Org. Chem.*, 1983, **48**, 4590.
2 R. K. Howe, B. R. Shelton and K. C. Liu, *J. Org. Chem.*, 1985, **50**, 903.
3 R. K. Howe and B. R. Shelton, *J. Org. Chem.*, 1990, **55**, 4603.
4 M. C. Aversa, G. Cum, G. Stagno d'Alcontres and N. Uccella, *J. Chem. Soc., Perkin Trans. 1*, 1972, 222.
5 A. Kerbal, J. Vebrel, M. Roche and B. Laude, *Tetrahedron Lett.*, 1990, **31**, 4145.
6 M. Msaddek, M. Rammah, G. Schmitt and J. Vebrel, *Bull. Soc. Chim. Belg.*, 1992, **101**, 323.
7 M. Msaddek, M. Rammah, K. Ciamala, J. Vebrel and B. Laude, *Synthesis*, 1997, 1495.
8 R. K. Howe and K. C. Liu, USP 4 364 768/1980; *Chem. Abstr.*, 1981, **94**, 47311h.
9 S. Rigolet, P. Goncalo, J. M. Melot and J. Vebrel, *J. Chem. Res.* (*M*), 1998, 2813.
10 N. Langlois, N. Van Bac, N. Dahuron, J. M. Delcroix, A. Deyine, D. Griffart-Brunet, A. Chiaroni and C. Riche, *Tetrahedron*, 1995, **51**, 3571.
11 N. Langlois, D. Griffart-Brunet, N. Van Bac, A. Chiaroni and C. Riche, *C.R. Seances Acad. Sci.*, 1995, **320**, 155.
12 J. H. Bailey, D. T. Cherry, K. H. Crapnell, M. G. Moloney and S. B. Shim, *Tetrahedron*, 1997, **53**, 11731.
13 P. Mitcuch, L. Fisera, V. Ondrus and P. Ertl, *Molecules*, 1997, **2**, 57.
14 P. Oravec, L. Fisera, I. Goljer and P. Ertl, *Monatsh. Chem.*, 1991, **122**, 977.
15 P. Oravec, L. Fisera, P. Ertl and D. Vegh, *Monatsh. Chem.*, 1991, **122**, 821.
16 J. P. Bouillon, Z. Janouzek, H. G. Viehe, B. Tinant and J. P. Declercq, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1853.
17 A. Strauss and H. H. Otto, *Helv. Chim. Acta*, 1997, **80**, 1823.
18 C. Wedler, B. Costisella and H. Schick, *J. Prakt. Chem.*, 1990, **332**, 557.
19 R. Huisgen, H. Hauck, R. Grashey and H. Seidl, *Chem. Ber.*, 1968, **101**, 2568.
20 H. Harikawa, T. Nishitani, T. Iwasaki and I. Inoue, *Tetrahedron Lett.*, 1979, **20**, 2193.
21 J. S. Splitter, T. M. Su, H. Ono and M. Calvin, *J. Am. Chem. Soc.*, 1971, **93**, 4075.
22 W. B. Jennings, D. R. Boyd and L. C. Waring, *J. Chem. Soc., Perkin Trans. 1*, 1976, 610.
23 A. Chiaroni, C. Riche, S. Rigolet, J. M. Melot and J. Vebrel, *Acta Crystallogr., Sect. C*, 2000, in the press.
24 K. B. G. Torssell, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH Verlagsgesellschaft, Weinheim, 1988, p. 36 and pp. 42–47.
25 F. Krönke and E. Börner, *Chem. Ber.*, 1936, **69**, 2006.
26 S. I. Murahashi, M. Mitsui, T. Shiota, T. Tsuda and S. Watanabe, *J. Org. Chem.*, 1990, **55**, 1736.
27 K. S. Chan, M. L. Yeung, W. K. Chan, R. J. Wang and T. F. C. Muk, *J. Org. Chem.*, 1995, **60**, 1741.
28 J. M. Cassady, G. A. Howe, J. M. Robinson and I. K. Stamos, *Org. Synth.*, 1983, **61**, 77.
29 M. Ueda and H. Mori, *J. Polym. Sci. Part A: Polym. Chem.*, 1990, **20**, 2597.
30 G. M. Ksander, J. E. McMurry and M. Johnson, *J. Org. Chem.*, 1977, **42**, 1180.
31 M. Ueda, M. Takahashi and T. Suzuki, *J. Polym. Sci., Polym. Phys. Ed.*, 1983, **20**, 1139.
32 J. Villiéras and M. Rambaud, *Synthesis*, 1982, 924.
33 N. El Alami, These de Doctorat, Université de Nantes, 1987.
34 N. El Alami, C. Belaud and J. Villiéras, *Tetrahedron Lett.*, 1987, **28**, 59.
35 D. L. Lee, C. J. Morrow and H. Rapoport, *J. Org. Chem.*, 1974, **39**, 893.
36 G. M. Sheldrick, a) *SHELXL86*, Program for Crystal Structure Solution, 1986; b) *SHELXL93*, Program for Crystal Structure Refinement, University of Göttingen, Germany, 1993.
37 *International Tables for X-Ray Crystallography*, ed., A. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1994.

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