Tetrahedron Vol. 49, No. 20, pp. 4267-4274, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Cycloaddition Reactions of 3,4-Dihydro-2*H*-pyrrole 1-Oxide with α,β-Unsaturated Lactones

David Alonso-Perarnau, Pedro de March,* Marta Figueredo, Josep Font,* and Angeles Soria

Departament de Química. Universitat Autònoma de Barcelona. 08193 Bellaterra. Spain.

(*Received in UK* 31 *December* 1992)

Abstract: The cycloadditions of nitrone **2** to α,β-unsaturated lactones **3-6** have been studied under several reaction conditions. The adducts derived from pentenolide **5** and hexenolide **6** are the first examples of the pyrano[3,4-*d*]pyrrolo[1,2-*b*]isoxazole and oxepino[3,4-*d*]pyrrolo[1,2-*b*]isoxazole systems respectively. The stereochemistry of the products has been established using high field nmr techniques. In all cases the major cycloadduct derives from an *exo* orientation of the transition state.

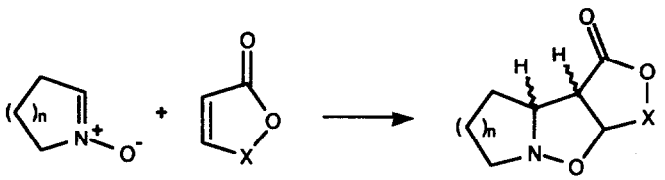
INTRODUCTION

The 1,3-dipolar cycloaddition reaction of nitrones to alkenes has become a potent synthetic methodology for the preparation of a wide variety of target molecules.[1] The isoxazolidines formed in this kind of concerted processes can incorporate multiple stereocenters with a complete control of their relative configuration and therefore a deep understanding of the stereochemical course of the cycloaddition is extremely important. In the last years, several groups are investigating in this field,[2] where two main difficulties have to be solved: the unmistakable assignment of the stereochemistry of the cycloadducts and the knowledge of the *E* or *Z* configuration of the nitrone in the reaction conditions. 2,3,4,5-Tetrahydropyridine 1-oxide, **1**, and 3,4-dihydro-2*H*-pyrrole 1-oxide, **2**, are the simplest representatives of two families of nitrones, that have been successfully used in the synthesis of several indolizidine[3] and pyrrolizidine[3a] classes of alkaloids, respectively. In the 1,3-dipolar reactions of these cyclic nitrones, which can not undergo *E*/*Z* isomerization, the stereochemical features of the cycloadducts evidence the stereoselectivity of the cycloaddition process, provided that the reaction is performed under kinetic control conditions. As part of a synthetic programme, we undertook a systematic study on the 1,3-dipolar cycloaddition of nitrones **1** and **2** to α,β-unsaturated lactones. In such reactions, the *endo* or *exo* orientation of the dipole and the dipolarophile in the transition state leads to tricyclic adducts with the ring fusion positions C_3 and C_4 (isoxazolidine numbering) in a *cis* or *trans* relationship, respectively (Scheme 1). We previously reported the results using nitrone **1** and demonstrated the importance of making a meticulous conformational analysis of the isoxazolidine cycloadducts.[2f] Here we wish to describe the 1,3-dipolar cycloaddition of nitrone **2** to butenolides **3** and **4**, pentenolide **5**, and hexenolide **6**.

RESULTS AND DISCUSSION

Among the methods described in the literature for the preparation of nitrone **2** the most convenient, in our hands, happened to be the oxidation of pyrrolidine with hydrogen peroxide in the presence of selenium dioxide

reported by Murahashi,[4] although we modified the purification procedure, since silica gel proved to be more efficient than alumina for the column chromatography of the crude product. The nitrone was kept in methylene chloride solution in the refrigerator for several days and the solvent evaporated immediately prior to use. In order to achieve a good degree of conversion with a high stereoselectivity, three different temperatures were investigated for the cycloaddition of nitrone **2** to each lactone. Table 1 summarizes reaction conditions and yields. All compounds obtained in these reactions have been analysed by high field nmr techniques, including COSY, ^{1}H-^{13}C correlation, and NOE experiments.



1, n = 2
2, n = 1

3, X = CH_2
4, X = $CHCH_3$
5, X = $(CH_2)_2$
6, X = $(CH_2)_3$

Scheme 1

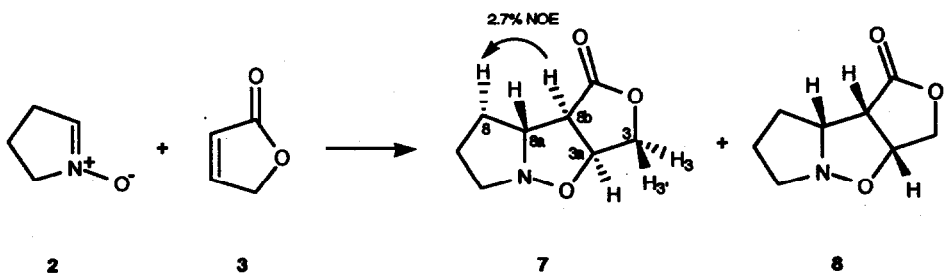
Table 1. Reactions of Nitrone **2** with α,β-Unsaturated Lactones **3**, **4**, **5**, and **6**.

entry	lactone	solvent/temp	reaction time	% yield [a]	*exo*/*endo*[b]	*anti*/*syn*[b]
1	**3**	$CHCl_3$ /20 °C	40 d	74 (86)	7	-
2	**3**	$CHCl_3$ /reflux	50 h	76 (84)	5	-
3	**3**	$PhCH_3$ /reflux	2 h	84 (88)	3	-
4	**4**	$CHCl_3$ /20 °C	40 d	70 (87)	6	11
5	**4**	$CHCl_3$ / reflux	50 h	76 (85)	4	8
6	**4**	$PhCH_3$/reflux	3 h	85 (86)	3	4
7	**5**	CH_2Cl_2 /20 °C	82 d	73	[c]	-
8	**5**	$CHCl_3$ / reflux	7d	86	85	-
9	**5**	$PhCH_3$ / reflux	22 h	88	43	-
10	**6**	$CHCl_3$ /20 °C	6 months	22 (74)	[c]	-
11	**6**	$CHCl_3$ / reflux	11 d	58 (78)	54	-
12	**6**	$PhCH_3$ / reflux	4 h	69 (87)	23	-

[a]Yield considering recovered lactone
[b]Determined by gc
[c]*Endo* adduct was not detected

The reaction between nitrone **2** and 2(5*H*)-furanone, **3**,[5] in chloroform at reflux (Scheme 2) was previously described by Tufariello and Tette.[6] These authors reported the isolation in a 43% yield of a single adduct with the regiochemistry depicted in **7** and **8**, but its *exo* (**7**) or *endo* (**8**) stereochemistry was not indicated. This and many other literature precedents demonstrate that nitrones add to electron-deficient unsymmetrically 1,2-disubstituted olefins in a regioselective manner affording isoxazolidines with the electron withdrawing group attached to the 4 position.[1,2f,2h,7] In fact, there is only a very recent work where small proportions of adducts with reversed regiochemistry have been also detected in the reactions between cyclic

nitrones and crotonates or cinnamates.[8] In our experiments, from the cycloaddition between **2** and **3** (Table 1, entries 1-3), after flash chromatography of the reaction crudes, two stereoisomers were isolated. The nmr data of both compounds are in agreement with the expected regiochemistry, since the β-carbonylic lactonic proton H_{3a} (δ 4.99 for **7**, δ 4.75 for **8**) resonates at higher chemical shift than the α-carbonylic proton H_{8b} (δ 3.50 for **7**, δ 3.73 for **8**). The most remarkable difference in the pmr spectra of **7** and **8** is the value of the coupling constant $J_{8a,8b}$: in the less polar major cycloadduct the observed value is 0 Hz, while in the minor one it is 9.4 Hz. Using the MM2 force field,[9] the geometries of **7** and **8** were optimized and the J values for each proton calculated. Due to the lack of parameters for the N-O assemblage, model compounds with a methine group instead of the nitrogen atom were used to evaluate the conformational distribution. With the geometries thus obtained, the nitrogen atom was placed back and the coupling constant values calculated with the 3JHH programme.[10] These values along with those experimentally obtained are given in Table 2. The comparison between the calculated and the observed values of $J_{8a,8b}$ in each compound indicates that the major adduct has most probably *exo* stereochemistry. This was corroborated by a NOE experiment: presaturation of the signal corresponding to H_{8b} in **7** caused a 2.7% enhancement of the signal at δ 1.74, associated to one of the protons attached to C_8. This observation is only compatible with the *exo* stereochemistry.

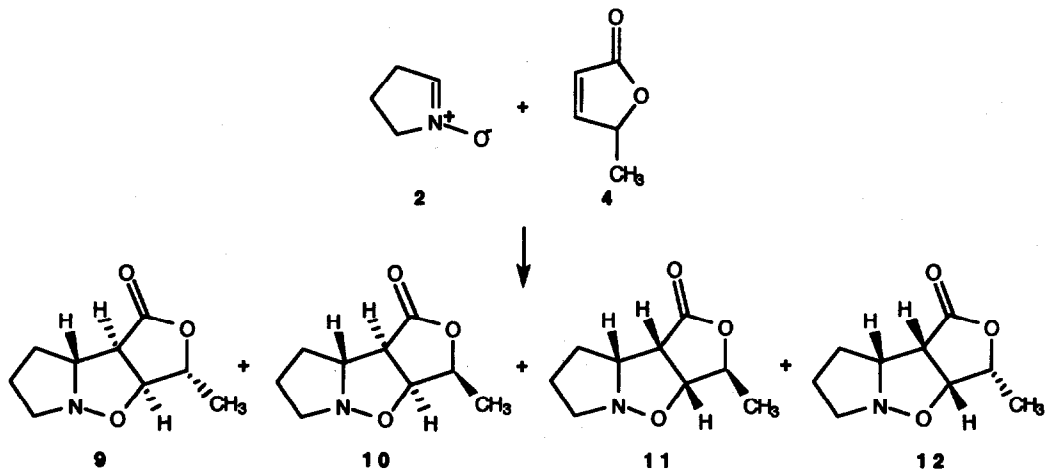


Scheme 2

Table 2. Experimental (d_6-acetone) and Calculated Coupling Constant Values for **7** and **8**.

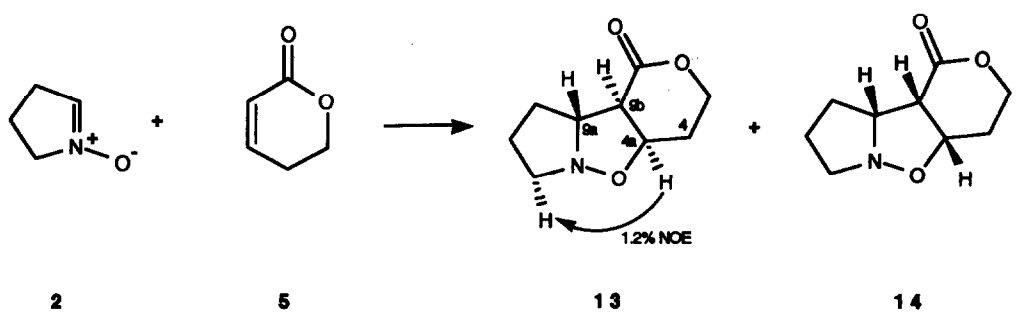
	$J_{3a,3}$	$J_{3a,3'}$	$J_{3a,8b}$	$J_{8a,8b}$	$J_{8a,8}$	$J_{8a,8}$
7, $J_{exp.}$	5.1	1.2	6.8	0	7.3	7.3
7, $J_{calc.}$	4.7	1.7	6.5	1.2	7.2	6.0
8, $J_{exp.}$	4.8	0.8	6.5	9.4	8.3	6.1
8, $J_{calc.}$	5.5	1.7	7.4	10.4	7.7	6.4

The reaction of nitrone **2** with 5-methyl-2(5*H*)-furanone, **4**,[11] (entries 4-6) afforded four cycloadducts, **9-12** (Scheme 3). Three of them were obtained in pure form and the other one, **10**, was isolated in 90% purity. Proton H_{3a} in major compound **9** and in **11** appears in the pmr spectra as a doublet ($J_{3a,8b}$=6.7 Hz) since $J_{3,3a}$ presents a value close to zero, which implies a *trans* relationship between H_3 and H_{3a}[12] indicating that these adducts arise from antifacial approaches of the reactants in the transition state. The observed $J_{8a,8b}$ for both **9** and **11** are 0 and 9.8 Hz respectively, and therefore adduct **9** was assigned the *exo* and adduct **11** the *endo* stereochemistry. The diastereoisomeric products **10** and **12** present $J_{3,3a}$ values of *ca.* 4.5 Hz, according with the relative *cis* geometry of H_3 and H_{3a} as a consequence of synfacial approaches in the transition states. Their *endo*/*exo* assignment was deduced as above from their $J_{8a,8b}$ values.



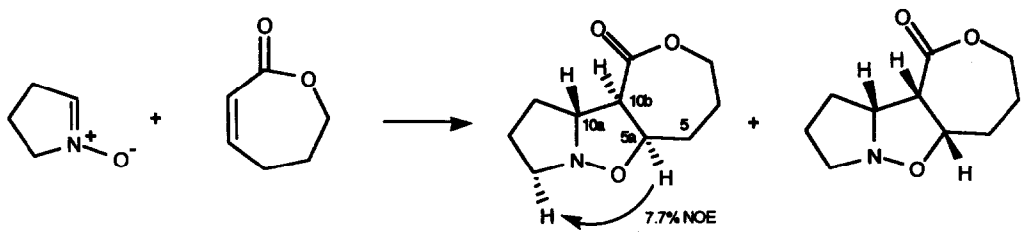
Scheme 3

The reaction of nitrone **2** with 5,6-dihydro-2-pyranone, **5**,[13] at room temperature (entry 7) gave a 73% yield of a unique compound identified as the *exo* cycloadduct **13**, the first example of a pyrano[3,4-*d*]pyrrolo[1,2-*b*]isoxazole system (Scheme 4). In this adduct proton H_{9b} absorbs at δ 3.30 as a doublet of doublets with $J_{9b,4a}$=7.8 Hz and $J_{9b,9a}$=3.6 Hz; this last small value points to a *trans* relationship between H_{9a} and H_{9b}, *i.e. exo* orientation of the transition state. NOE experiments are in agreement with this assignment: irradiation of the signal corresponding to H_{9b} does not enhance the absorption due to H_{9a} (δ 3.83) and presaturation of H_{4a} (δ 4.70) causes a 1.2% NOE on H_7 (δ 3.04). Moreover, when the same cycloaddition was run at higher temperatures (entries 8 and 9) we were able to isolate small quantities of a diastereoisomeric cycloadduct with $J_{9a,9b}$=8.5 Hz, value which is consistent with the *cis* relationship between these protons, *i.e.* the *endo* stereoisomer **14**.



Scheme 4

Very similar results were obtained in the cycloaddition of nitrone **2** to 6,7-dihydro-2(5*H*)-oxepinone, **6**,[14] (entries 10-12). The major product obtained in these reactions presented $J_{10a,10b}$=4.6 Hz; it was assigned as the *exo* adduct **15** based on the 7.7% NOE observed on the signal corresponding to the protons attached to C_8 upon irradiation of H_{5a} at δ 4.55 (Scheme 5). Compound **15** and its *endo* isomer **16** are the first examples of an oxepino[3,4-*d*]pyrrolo[1,2-*b*]isoxazole system.



2 **6** **15** **16**

Scheme 5

The results summarized in Table 1 show that the reactivity of the dipolarophiles decreases on increasing the size of the lactone ring. Longer reaction times are necessary to obtain similar conversions on passing from butenolides **3** and **4** to pentenolide **5** and hexenolide **6**. Although in all cases the *exo* transition state is favoured over the *endo*, the stereoselectivity of the cycloaddition is higher with the more sterically demanding lactones **5** and **6**. Interestingly, comparison of these cycloadditions with those performed using nitrone **1**[2f,7e] indicates that the last are more stereoselective. This can be rationalized in terms of the smaller destabilization of the *endo vs.* the *exo* transition state in the cycloadditions of the less reactive[15] but more planar nitrone **2**.

EXPERIMENTAL SECTION

Commercial grade solvents were used without further purification. The unsaturated lactones were prepared according to previously described methods: **3**,[5] **4**,[11] **5**,[13] and **6**.[14] Reaction mixtures were stirred magnetically. The organic extracts were dried over anhydrous sodium sulphate. Reaction solutions were concentrated using a rotary evaporator at 15-20 Torr. Flash column chromatographies were performed by using silica gel (230-400 mesh). Melting points have been determined on a Kofler hot stage and are corrected. The ir spectra were recorded on a Nicolet 5 ZDX spectrophotometer. The 400 MHz pmr and 100 MHz cmr spectra were recorded on Bruker AM-400-WB or AC-400-NB instruments; chemical shifts are given in ppm relative to TMS (δ values). Electron impact mass spectra (70 eV) and gc-ms analyses were recorded on a Hewlett-Packard 5985B gc-ms system; only peaks with higher intensity than 20% are reported, unless they belong to molecular ions or to significant fragments.

*3,4-Dihydro-2*H*-pyrrole 1-oxide*, **2**

This nitrone was prepared by the reported method of Murahashi *et al.*,[4] but the purification procedure was modified: the crude product was chromatographed on a silica gel column using chloroform-methanol 9:1 as eluent, the yield was 64%.

*Cycloaddition of nitrone **2** to 2(5*H*)-furanone*, **3**

A solution of **2** (710 mg, 8.3 mmol) in chloroform (5 mL) was treated with a solution of **3** (572 mg, 6.8 mmol) in chloroform (10 mL) at room temperature for 40 days. Removal of the solvent gave 1.383 g of crude product, that was submitted to flash chromatography affording the following fractions: i) 84 mg (15%) of starting lactone using methylene chloride-ether 9:1 as eluent; ii) 736 mg (64%) of (3a*R**,8a*S**,8b*S**)-octahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1-one, **7**, with the same eluent; and iii) 113 mg (10%) of (3a*R**,8a*R**,8b*S**)-octahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1-one, **8**, with chloroform-methanol 9:1 as mobile phase. **7**: mp 92-93 °C (hexane) [lit.[6] 87-89 °C]; ir (KBr) 2990, 2968, 1755, 1186, 1081 cm^{-1}; pmr (d_6-acetone) 4.99 (ddd, $J_{3a,8b}$=6.8 Hz, $J_{3a,3}$=5.1 Hz, $J_{3a,3}$=1.2 Hz, 1H, H_{3a}), 4.44 (dd, $J_{3,3}$=10.4 Hz, $J_{3,3a}$=5.1 Hz, 1H, H_3), 4.22 (dd, $J_{3,3}$=10.4 Hz, $J_{3,3a}$=1.2 Hz, 1H, H_3), 3.73 (t, $J_{8a,8}\approx J_{8a,8}\approx$7.3 Hz, 1H,

H_{8a}), 3.50 (d, $J_{8b,3a}$=6.8 Hz, 1H, H_{8b}), 3.23 (ddd, $J_{6,6}$=13.2 Hz, $J_{6,7}$=7.8 Hz, $J_{6,7}$=4.4 Hz, 1H, H_6), 2.99 (dt, $J_{6,6}$=13.2 Hz, $J_{6,7}\approx J_{6,7}\approx$8.0 Hz, 1H, H_6), 2.07 (m, 1H, H_8), 1.98 (m, 1H, H_7), 1.78-1.70 (m, 2H, H_7, H_8); cmr (d_6-acetone) 177.4 (C_1), 77.3 (C_{3a}), 73.8 (C_3), 70.9 (C_{8a}), 56.8 (C_6), 55.2 (C_{8b}), 30.7 (C_8), 24.9 (C_7); ms *m/e* (%) 169 (M^+, 13), 85 (100), 55 (73), 41 (22). Anal. Calcd. for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.96; H, 6.60; N, 8.32. **8**: mp 46-47 °C (hexane); ir (KBr) 2966, 1762, 1462, 1184, 1067 cm^{-1}; pmr (d_6-acetone) 4.75 (ddd, $J_{3a,8b}$=6.5 Hz, $J_{3a,3}$=4.8 Hz, $J_{3a,3}$=0.8 Hz, 1H, H_{3a}), 4.39 (dd, $J_{3,3}$=10.8 Hz, $J_{3,3a}$=4.8 Hz, 1H, H_3), 4.20 (brd, $J_{3,3}$=10.8 Hz, 1H, H_3), 3.90 (ddd, $J_{8a,8b}$=9.4 Hz, $J_{8a,8}$=8.3 Hz, $J_{8a,8}$=6.1 Hz, 1H, H_{8a}), 3.73 (dd, $J_{8b,8a}$=9.4 Hz, $J_{8b,3a}$=6.5 Hz, 1H, H_{8b}), 3.22 (ddd, $J_{6,6}$=13.5 Hz, $J_{6,7}$=7.2 Hz, $J_{6,7}$=3.6 Hz, 1H, H_6), 2.87 (dt, $J_{6,6}$=13.5 Hz, $J_{6,7}\approx J_{6,7}\approx$7.5 Hz, 1H, H_6), 2.00 (m, 1H, H_8), 1.90 (m, 1H, H_7), 1.82-1.66 (m, 2H, H_7, H_8); cmr (d_6-acetone) 176.1 (C_1), 79.5 (C_{3a}), 70.4 (C_3), 68.6 (C_{8a}), 56.3 (C_6), 53.0 (C_{8b}), 26.8 (C_8), 25.0 (C_7); ms *m/e* (%) 169 (M^+, 12), 85 (100), 55 (69), 41 (20). Anal. Calcd. for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.73; H, 6.49; N, 8.26.

The same reaction was performed in chloroform at reflux for 50 h yielding 63% and 13% of **7** and **8** respectively. The yield raises to 84% considering the recovered starting lactone. A 84% yield was obtained when the reaction was conducted in toluene at reflux for 2 h.

Cycloaddition of nitrone **2** *to 5-methyl-2(5H)-furanone,* **4**

A mixture of 577 mg (6.8 mmol) of **2** and 545 mg (5.6 mmol) of 5-methyl-2(5*H*)-furanone, **4**, in 15 mL of chloroform was left at 20 °C for 40 d. Flash chromatography of the crude afforded the following fractions: i) 106 mg (19%) of **4** using methylene chloride-ether 9:1 as eluent; ii) 588 mg (58%) of (3*R**,3a*S**,8a*R**,8b*R**)-octahydro-3-methylfuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1-one, **9**, and its (3*R**,3a*R**,8a*S**,8b*S**)- diastereoisomer, **10**, with the same eluent; iii) 83 mg (8%) of the (3*R**,3a*S**,8a*S**,8b*R**)-isomer, **11**, with $CHCl_3$-methanol 9:1 as mobile phase; and iv) 41 mg (4%) of a mixture of **11** and its (3*R**,3a*R**,8a*R**,8b*S**)-isomer, **12**, using the same eluent. An analytical sample of **9** was obtained by repeated crystallization. Isomer **12** was purified by repeated chromatography. **9**: white solid, mp 78-79 °C (hexane); ir (KBr) 2989, 2952, 1762, 1189, 1032 cm^{-1}; pmr (d_6-acetone) 4.57 (brd, $J_{3a,8b}$=6.7 Hz, 1H, H_{3a}), 4.50 (dq, $J_{3,Me}$=6.7 Hz, $J_{3,3a}$=1.2 Hz, 1H, H_3), 3.73 (t, $J_{8a,8}\approx J_{8a8}\approx$7.6 Hz, 1H, H_{8a}), 3.61 (d, $J_{8b,3a}$=6.7 Hz, 1H, H_{8b}), 3.22 (ddd, $J_{6,6}$=13.4 Hz, $J_{6,7}$=7.3 Hz, $J_{6,7}$=3.7 Hz, 1H, H_6), 2.98 (dt, $J_{6,6}$=13.4 Hz, $J_{6,7}$=$J_{6,7}$=7.9 Hz, 1H, H_6), 2.06 (m, 1H, H_8), 1.96 (m, 1H, H_7), 1.77-1.65 (m, 2H, H_7, H_8), 1.32 (d, $J_{Me,3}$=6.7 Hz, 3H, Me); cmr (d_6-acetone) 176.7 (C_1), 82.6 (C_{3a}), 82.0 (C_3), 70.7 (C_{8a}), 56.8 (C_6), 55.3 (C_{8b}), 30.6 (C_8), 24.8 (C_7), 19.7 (Me); ms *m/e* (%) 183 (M^+, 15), 85 (100), 70 (43), 55 (94), 41 (32). Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.21; H, 7.21; N, 7.67. **10**: oil (90% purity), pmr (d_6-acetone) 4.80 (dd, $J_{3a,8b}$=6.7 Hz, $J_{3a,3}$=4.6 Hz, 1H, H_{3a}), 4.66 (dq, $J_{3,Me}$=6.7 Hz, $J_{3,3a}$=4.6 Hz, 1H, H_3), 3.74 (t, $J_{8a,8}$=$J_{8a,8}$=7.3 Hz, 1H, H_{8a}), 3.62 (d, $J_{8b,3a}$=6.7 Hz, 1H, H_{8b}), 3.26 (ddd, $J_{6,6}$=13.4 Hz, $J_{6,7}$=7.6 Hz, $J_{6,7}$=4.3 Hz, 1H, H_6), 2.96 (dt, $J_{6,6}$=13.4 Hz, $J_{6,7}$=$J_{6,7}$=7.9 Hz, 1H, H_6), 2.10-1.93 (m, 2H, H_7, H_8), 1.80-1.64 (m, 2H, H_7, H_8), 1.35 (d, $J_{Me,3}$=6.7 Hz, 3H, Me); cmr (d_6-acetone) 176.9 (C_1), 79.8/78.4 (C_3/C_{3a}), 70.8 (C_{8a}), 57.0 (C_6), 57.0 (C_{8b}), 30.3 (C_8), 24.9 (C_7), 14.5 (Me) ms *m/e* (%) 183 (M^+, 18), 86 (39), 85 (100), 55 (76), 41 (26). **11**: white solid, mp 76-77 °C (hexane); ir (KBr) 2986, 2945, 1769, 1352, 1187, 990 cm^{-1}; pmr (d_6-acetone) 4.49 (q, $J_{3,Me}$=6.7 Hz, 1H, H_3), 4.37 (d, $J_{3a,8b}$=6.7 Hz, 1H, H_{3a}), 3.89 (brdt, $J_{8a,8b}\approx J_{8a,8}\approx$8.8 Hz, $J_{8a,8}$=5.8 Hz, 1H, H_{8a}), 3.84 (dd, $J_{8b,8a}$=9.8 Hz, $J_{8b,3a}$=6.7 Hz, 1H, H_{8b}), 3.21 (ddd, $J_{6,6}$=13.4 Hz, $J_{6,7}$=7.0 Hz, $J_{6,7}$=3.6 Hz, 1H, H_6), 2.86 (ddd, $J_{6,6}$=13.4 Hz, $J_{6,7}$=8.6 Hz, $J_{6,7}$=7.3 Hz, 1H, H_6), 2.01 (m, 1H, H_8), 1.87 (m, 1H, H_7), 1.82-1.66 (m, 2H, H_7, H_8), 1.32 (d, $J_{Me,3}$=6.7 Hz, 3H, Me); cmr (d_6-acetone) 175.5 (C_1), 84.5 (C_{3a}), 78.7 (C_3), 68.4 (C_{8a}), 56.3 (C_6), 52.8 (C_{8b}), 26.8 (C_8), 24.9 (C_7), 19.9 (Me); ms *m/e* (%) 183 (M^+, 12), 85 (100), 55 (68), 41 (22). Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.23; H, 7.26; N, 7.70. **12**: oil, pmr (d_6-acetone) 4.67 (dq, $J_{3,Me}$=6.7 Hz, $J_{3,3a}$=4.3 Hz, 1H, H_3), 4.59 (dd, $J_{3a,8b}$=6.7 Hz, $J_{3a,3}$=4.3 Hz, 1H, H_{3a}), 3.90 (dt, $J_{8a,8b}\approx J_{8a,8}\approx$9.0 Hz, $J_{8a,8}$=5.5 Hz, 1H, H_{8a}), 3.78 (dd, $J_{8b,8a}$=9.8 Hz, $J_{8b,3a}$=6.7 Hz, 1H, H_{8b}), 3.22 (ddd, $J_{6,6}$=13.4 Hz, $J_{6,7}$=7.3 Hz, $J_{6,7}$=3.7 Hz, 1H, H_6), 2.86 (ddd, $J_{6,6}$=13.4 Hz, $J_{6,7}$=8.6 Hz, $J_{6,7}$=7.3 Hz, 1H,

H_6), 2.08 (m, 1H, H_8), 1.87 (m, 1H, H_7), 1.81-1.64 (m, 2H, H_7, H_8), 1.30 (d, $J_{Me,3}$=6.7 Hz, 3H, Me); cmr (d_6-acetone) 175.5 (C_1), 80.8 (C_{3a}), 76.7 (C_3), 68.7 (C_{8a}), 56.3 (C_6), 54.7 (C_{8b}), 26.7 (C_8), 24.9 (C_7), 14.4 (Me); ms *m/e* (%) 183 (M^+, 15), 86 (43), 85 (100), 55 (69), 41 (21).

The same reaction was performed in chloroform at reflux for 50 h yielding 76% of cycloadducts **9-12**. The yield raises to 85% considering the recovered starting lactone. A 85% yield was obtained when the reaction was conducted in toluene at reflux for 3 h.

Cycloaddition of nitrone **2** *to 5,6-dihydro-2-pyranone,* **5**

A solution of **2** (271 mg, 3.2 mmol) in 25 mL of methylene chloride was treated with 5,6-dihydro-2-pyranone, **5**, for 82 days at room temperature. Flash chromatography of the crude (610 mg) using chloroform-methanol 9:1 as eluent afforded 355 mg (73%) of (4a*R**,9a*R**,9b*R**)-octahydro-1*H*-pyrano[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1-one, **13**: mp 50-51 °C (hexane); ir (KBr) 2972, 2943, 1729, 1270, 1071 cm^{-1}; pmr (d_6-acetone) 4.70 (brdt, $J_{4a,9b}$=7.8 Hz, $J_{4a,4}\approx J_{4a,4}\approx$5.2 Hz, 1H, H_{4a}), 4.40 (ddd, $J_{3,3}$=11.3 Hz, $J_{3,4}$=8.2 Hz, $J_{3,4}$=3.3 Hz, 1H, H_3), 4.20 (dddd, $J_{3,3}$=11.3 Hz, $J_{3,4}$=7.2 Hz, $J_{3,4}$=3.4 Hz, $J_{3,4a}$=0.8 Hz, 1H, H_3), 3.83 (ddd, $J_{9a,9}$=8.3 Hz, $J_{9a,9}$=4.9 Hz, $J_{9a,9b}$=3.6 Hz, 1H, H_{9a}), 3.30 (dd, $J_{9b,4a}$=7.8 Hz, $J_{9b,9a}$=3.6 Hz, 1H, H_{9b}), 3.04 (m, 2H, 2xH_7), 2.13 (dddd, $J_{4,4}$=14.7 Hz, $J_{4,3}$=8.2 Hz, $J_{4,4a}$=5.2 Hz, $J_{4,3}$=3.4 Hz, 1H, H_4), 2.08 (m, 1H, H_9), 1.96 (m, 1H, H_8), 1.86-1.77 (m, 2H, H_9, H_4), 1.71 (m, 1H, H_8); cmr (d_6-acetone) 171.2 (C_1), 73.3 (C_{4a}), 70.1 (C_{9a}), 65.1 (C_3), 55.8 (C_7), 54.5 (C_{9b}), 30.3 (C_9), 28.3 (C_4), 23.8 (C_8); ms *m/e* (%) 183 (M^+, 14), 99 (20), 85 (100), 83 (20), 68 (41), 55 (72), 41 (38). Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.35; H, 7.46; N, 7.66.

When the reaction was performed in chloroform at reflux for 7 days a 85% yield of **13** along with a 1% mixture of **13** and its diastereisomer (4a*R**,9a*S**,9b*R**), **14**, were obtained. The cycloaddition run in toluene at reflux during 22 h allowed the isolation of 86% yield of **13**, 1% of a mixture of **13** and **14**, and 1% of pure **14**: pmr (d_6-acetone) 4.32 (m, 2H, H_3, H_{4a}), 4.23 (m, 1H, H_3), 3.86 (q, $J_{9a,9b}\approx J_{9a,9}\approx J_{9a,9}\approx$8.5 Hz, 1H, H_{9a}), 3.78 (t, $J_{9b,4a}\approx J_{9b,9a}\approx$8.5 Hz, 1H, H_{9b}), 3.36 (ddd, $J_{7,7}$=13.4 Hz, $J_{7,8}$=7.3 Hz, $J_{7,8}$=3.7 Hz, 1H, H_7), 2.94 (dt, $J_{7,7}$=13.4 Hz, $J_{7,8}\approx J_{7,8}\approx$8.5 Hz, 1H, H_7), 2.05 (m, 1H, H_9), 1.95-1.65 (m, 4H), 1.49 (m, 1H); cmr (d_6-acetone) 170.5 (C_1), 73.6 (C_{4a}), 69.8 (C_{9a}), 65.1 (C_3), 56.3 (C_7), 52.4 (C_{9b}), 29.0 (C_9), 27.3 (C_4), 24.7 (C_8); ms *m/e* (%) 183 (M^+, 13), 99 (22), 85 (100), 55 (55), 41 (25).

Cycloaddition of nitrone **2** *to 6,7-dihydro-2(5H)-oxepinone,* **6**

A solution of **2** (380 mg, 4.5 mmol) in chloroform (5 mL) was treated with a solution of **6** (336 mg, 3.0 mmol) in chloroform (10 mL) at room temperature for 4 months. After this period 255 mg of **2** (3.0 mmol) were added. Removal of the solvent after 6 months of reaction time gave 1.086 g of crude product, that was submitted to chromatography using methylene chloride-ether 9:1 as eluent and affording the following fractions: i) 235 mg (62%) of starting lactone **6**; and ii) 131 mg (22%; if the recovered lactone is considered the yield raises to 74%) of (5a*R**,10a*R**,10b*R**)-decahydrooxepino[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1-one, **15**: mp 108-109 °C (hexane); ir (KBr) 2943, 2870, 1728, 1165 cm^{-1}; pmr (d_6-acetone) 4.55 (ddd, $J_{5a,5}$=12.5 Hz, $J_{5a,10b}$=9.2 Hz, $J_{5a,5}$=3.5 Hz, 1H, H_{5a}), 4.42 (dt, $J_{3,3}=J_{3,4}$=12.8 Hz, $J_{3,4}$=4.6 Hz, 1H, H_3), 4.20 (dd, $J_{3,3}$=12.8 Hz, $J_{3,4}$=6.7 Hz, 1H, H_3), 4.16 (dt, $J_{10a,10}$=7.6 Hz, $J_{10a,10b}\approx J_{10a,10}\approx$4.0 Hz, 1H, H_{10a}), 3.76 (dd, $J_{10b,5a}$=9.2 Hz, $J_{10b,10a}$=4.6 Hz, 1H, H_{10b}), 3.10-2.96 (m, 2H, 2xH_8), 2.10-1.91 (m, 4H, H_4, H_5, H_9, H_{10}), 1.89-1.65 (m, 3H, H_4, H_9, H_{10}), 1.42 (ddt, J=13.3 Hz, J'=$J_{5,5a}$=12.5 Hz, $J_{5,4}$=6.2 Hz, 1H, H_5); cmr (d_6-acetone) 172.7 (C_1), 74.9 (C_{5a}), 67.9 (C_{10a}), 65.2 (C_3), 57.8 (C_{10b}), 54.3 (C_8), 29.5 (C_{10}), 26.9 (C_5), 23.5/23.4 (C_4/C_9); ms *m/e* (%) 197 (M^+, 11), 110 (39), 109 (27), 86 (29), 85 (71), 83 (47), 71 (78), 69 (30), 68 (32), 55 (71), 43 (37), 42 (40), 41 (100). Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 61.09; H, 7.67; N, 7.12.

The reaction was performed in chloroform at reflux for 11 days, allowing the isolation of **15** in 52% yield and a 6% yield of its diastereoisomer (5a*R**,10a*S**,10b*R**), **16**, using chloroform-methanol 9:1 as eluent in the chromatography. When this cycloaddition was run in toluene at reflux for 4 h, compounds **15** and **16** were isolated in 65 and 4% yield respectively. **16**: pmr (d_6-acetone) 4.3-4.0 (m, 4H, H_{5a}, 2xH_3, H_{10b}),

3.60 (dt, J=8.9 Hz, J'≈J"≈7.6 Hz, 1H, H_{10a}), 3.30 (ddd, $J_{8,8}$=14.0 Hz, $J_{8,9}$=8.6 Hz, $J_{8,9}$=3.4 Hz, 1H, H_8), 2.95 (dt, $J_{8,8}$=14.0 Hz, $J_{8,9}$≈$J_{8,9}$≈8.8 Hz, 1H, H_8), 2.15 (m, 1H), 2.10-1.90 (m, 3H), 1.80-1.60 (m, 3H), 1.46 (m, 1H); cmr (d_6-acetone) 172.4 (C_1), 74.7, 70.4, 65.7, 55.9, 55.2, 29.1, 27.6, 24.1, 23.7; ms *m/e* (%) 197 (M^+, 10), 113 (25), 85 (100), 71 (22), 55 (39), 41 (30).

Acknowledgements: We gratefully acknowledge the "Ministerio de Educación y Ciencia" for financial support through "Dirección General de Investigación Cientffica y Técnica" (project PB89-0287) and a grant to A. S. from the "Comissió Interdepartamental de Recerca i Innovació Tecnológica".

REFERENCES

1. a) Tufariello, J. J. *1,3-Dipolar Cycloaddition Chemistry*; John Wiley and Sons, Inc.: New York, 1984; Vol. 2. Chapt. 9; b) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH Verlagsgesellschaft: Weinheim, 1988.
2. a) Ali, Sk. A.; Wazeer, M. I. M.; Mazhar-Ul-Haque, *Tetrahedron* **1990**, *46*, 7207-7218; b) Burdisso, M.; Gandolfi, R.; Grünanger, P.; Rastelli, A. *J. Org. Chem.* **1990**, *55*, 3427-3429; c) Annunziata, R.; Cinquini, M.; Cozzi, F.; Giaroni, P.; Raimondi, L. *Tetrahedron Lett.* **1991**, *32*, 1659-1662; d) DeShong, P.; Li, W.; Kennington, Jr., J. W.; Ammon, H. L. *J. Org. Chem.* **1991**, *56*, 1364-1373; e) Norman, B. H.; Gareau, Y.; Padwa, A. *J. Org. Chem.* **1991**, *56*, 2154-2161; f) Cid, P.; de March, P.; Figueredo, M.; Font, J.; Milán, S. *Tetrahedron Lett.* **1992**, *33*, 667-670; g) Ito, M.; Maeda, M.; Kibayashi, C. *Tetrahedron Lett.* **1992**, *33*, 3765-3768; h) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 6929-6952; i) Blake, A. J.; Cook, T. A.; Forsyth, A. C.; Gould, R. O.; Paton, R. M. *Tetrahedron* **1992**, *48*, 8053-8064.
3. a) Confalone, P. N.; Huie, E. M. *Organic Reactions*; John Wiley and Sons, Inc.: New York, 1988; Vol. 36. Chapt. 1; b) Grundon, M. F. *Nat. Prod. Rep.* **1989**, *6*, 523-536; c) Cordero, F. M.; Brandi, A.; Querci, C.; Goti, A.; de Sarlo, F.; Guarna, A. *J. Org. Chem.* **1990**, *55*, 1762-1767; d) Michael, J. P. *Nat. Prod. Rep.* **1990**, *7*, 485-513.
4. Murahashi, S.-I.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 2383-2386.
5. Price, C. C.; Judge, J. M. *Organic Synthesis*; John Wiley and Sons: New York, 1973; Coll. Vol. 5, pp. 255-258.
6. Tufariello, J. J.; Tette, J. P. *J. Org. Chem.* **1975**, *40*, 3866-3869.
7. a) de Lange, B.; Feringa, B. L. *Tetrahedron Lett.* **1988**, *29*, 5317-5320; b) Blake, A. J.; Forsyth, A. C.; Paton, R. M. *J. Chem. Soc., Chem. Commun.* **1988**, 440-442; c) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Gazz. Chim. Ital.* **1989**, *119*, 253-269; d) Figueredo, M.; Font, J.; de March, P. *Chem. Ber.* **1989**, *122*, 1701-1704; *ibid.* **1990**, *123*, 1595; e) Cid, P.; Figueredo, M.; Font, J.; Jaime, C.; de March, P.; Virgili, A. *Magn. Reson. Chem.* **1990**, *28*, 947-951; f) Olsson, T.; Stern, K.; Westman, G. *Tetrahedron* **1990**, *46*, 2473-2482; g) Panfil, I.; Belzecki, C.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron* **1991**, *47*, 10087-10094.
8. Ali, Sk. A.; Perzanowski, H. P. *J. Chem. Res., Synop.* **1992**, 146-147.
9. Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127-8134.
10. Jaime, C; Osawa, E. *QCPE* **1983**, programme 12, 461.
11. Ortuño, R. M.; Cardellach, J.; Font, J. *J. Heterocycl. Chem.* **1987**, *24*, 79-84.
12. a) Fariña, F.; Martín, M. V.; Sánchez, F. *Heterocycles* **1986**, *24*, 2587-2592; b) Jaime, C.; Ortuño, R. M.; Font, J. *J. Org. Chem.* **1986**, *51*, 3946-51; *ibid* **1987**, *52*, 5600.
13. Nakagawa, M.; Tonozuka, M.; Obi, M.; Kiuchi, M.; Hino, T. *Synthesis* **1974**, 510-511.
14. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434-5447; Chow, H.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1815-1819.
15. Ali, Sk. A.; Khan, J. H.; Wazeer, M. I. M.; Perzanowski, H. P. *Tetrahedron* **1989**, *45*, 5979-5986.