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Cycloaddition Reactions of *C,N*-Diphenylnitrone to Methylene-γ-butyrolactones

Martina Cacciarini, Franca M. Cordero, Cristina Faggi and Andrea Goti*

Dipartimento di Chimica Organica "Ugo Schiff", Centro di studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni (CSCEA) C. N. R., Università di Firenze, via G. Capponi 9, I-50121 Firenze, Italy
Fax: +39 055 2476964, E-mail: goti@chimorg.unifi.it

*Author to whom correspondence should be addressed.

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Abstract: Cycloaddition of *C,N*-diphenylnitrone to α-methylene-γ-butyrolactone afforded two diastereomeric 5-spirosubstituted isoxazolidines with high selectivity. Structural assignment was ascertained by NMR studies and an X-ray diffraction experiment on a single crystal of the major isomer and the diastereoselectivity was rationalized on examination of the alternative transition states leading to the two diastereoisomers.

Keywords: Nitrones, lactones, 1,3-dipolar cycloaddition, stereoselectivity, regioselectivity.

Introduction

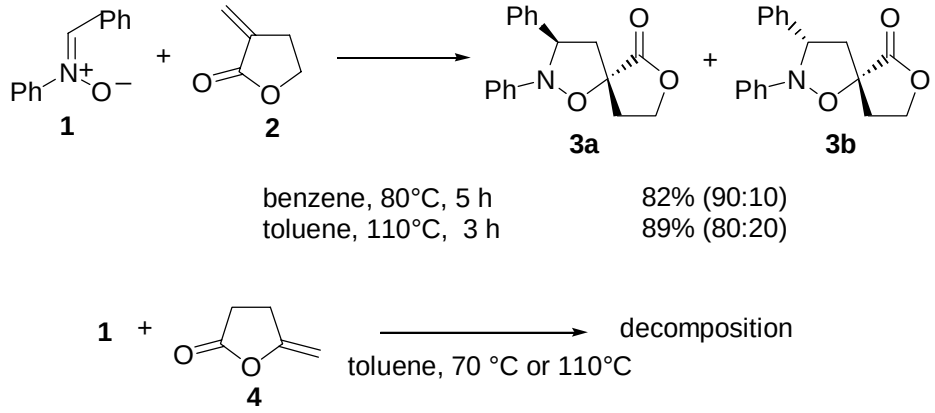
During the last two decades the nitrone cycloaddition to alkenes has emerged as one of the most versatile methods for the construction of complex nitrogen heterocycles by manipulation of the primary saturated isoxazole cycloadducts [1]. In this context, our research group has been active in the synthesis of variously spiro-cyclized isoxazolidines and isoxazolines as intermediates to a series of functionalized heterocycles, including pyridones, azepinones, indolizinones, quinolizinones, through an original protocol involving the thermal rearrangement of the strained isoxazole derivatives [2]. The 5-spiro cycloadducts were synthesized by cycloaddition of nitrones or nitrile oxides to alkylidenecyclopropanes [3] or –butanes [4]. 4,5-Dispirocyclopropane and 3-spirocyclobutane isoxazole derivatives

have also been obtained by cycloaddition of bicyclopropylidene [5] or *N*-methylcyclobutylideneamine *N*-oxide [6], respectively.

Recently, de March, Font, and coworkers have reported the synthesis of 2-spirocyclized perhydropyrrolo[1,2-*b*]isoxazole derivatives by cycloaddition of *exo*-methylenebutyrolactones to a cyclic nitrone, pyrroline *N*-oxide [7]. These data prompt us to report our own results on the cycloaddition of an acyclic nitrone, namely *C*,*N*-diphenylnitrone, to α– and γ–methylenebutyrolactone. Our study complements the Spanish group's one, constituting the first example of cycloaddition of *exo*-substituted methylene lactones to acyclic nitrones [8], the only previous example being on a cyclic one [7], in contrast to the nitrone cycloadditions to *endo*-substituted unsaturated lactones, which have been studied in greater detail [7,9].

Results and Discussion

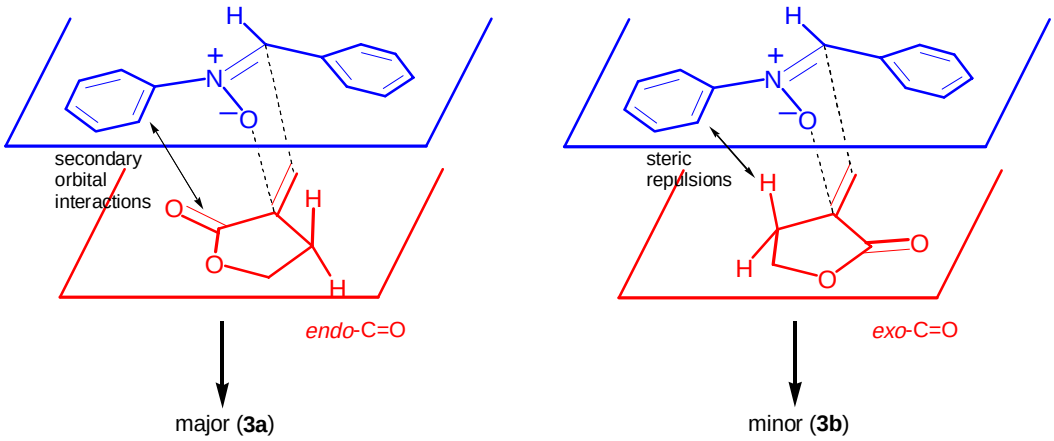
The reaction of *C*,*N*-diphenylnitrone (**1**) with α-methylene-γ-butyrolactone (**2**), carried out in refluxing benzene or toluene as solvent, required 5 h and 3 h, respectively, for completion and afforded in both cases two products, which were assigned the diastereomeric structures **3** (Scheme 1). On the contrary, reaction of the same nitrone **1** with γ-methylene-γ-butyrolactone (**4**) at either 110°C or 70°C in toluene, gave only tars deriving from decomposition and polymerization of starting materials, confirming the already observed much lower reactivity of **4** with respect to **2** [7].



Scheme 1. Reactions of nitrone **1** with methylenebutyrolactones **2** and **4**.

The ratio of products formed in the cycloaddition of nitrone **1** with **2** (evaluated by integration from 500 MHz ^{1}H NMR spectra of the crude reaction mixtures) depends on the reaction conditions, increasing on lowering the temperature (Scheme 1). However, for practical reasons, the boiling temperature of benzene represents a good compromise between selectivity and reactivity: a good 9:1 ratio of products was obtained after 5 h. The major product spontaneously and selectively crystallizes upon concentration of the mixture and can be obtained as a pure solid. The mother liquor consisted of a mixture of **3** enriched in the minor diastereoisomer which could be, at least partially, separated by flash

column chromatography, with isolation of a pure sample of **3b** for characterization and structural assignment purposes. Both isomers turned out to be 5-spirocyclic isoxazolidines, deriving from a complete regioselectivity of the cycloaddition, as expected on the basis of previous results [7] and FMO considerations [1a,10]. The assignment of the structures as 5-disubstituted isoxazolidines **3** was straightforward on the basis of the lack of the deshielded protons on the 5-position of isoxazolidine and the multiplicity of the protons of this heterocycle (AMX spin system) in the ^{1}H NMR spectra and the signals for C-5' and C-4' carbon atoms of the isoxazolidine, which appear as a quaternary carbon and a methylene, respectively, in the ^{13}C NMR spectra of both isomers **3**. Much less obvious was the assignment of the relative configuration to the stereogenic centers in the two diastereoisomers **3a** and **3b**. The observed high stereoselectivity is consistent with the selectivity obtained in the cycloaddition of pyrroline *N*-oxide to the same lactone **2** [7]. However, the present case is complicated by the possible *E*-*Z* equilibration of acyclic nitrones [1a,11]. *C*-Alkyl and *C*-aryl acyclic nitrones are usually assumed to undergo cycloadditions as the most stable *Z* diastereoisomer [1a,11], in contrast to cyclic nitrones, which must react in the only available *E* form. Indeed, the time required for *E*-*Z* interconversion is usually long [11,12] even at high temperatures, consistently with calculated activation energies of more than 30 kcal/mol [1d]. This case complements therefore the reported one with the cyclic nitrone [7].



Scheme 2. Transition state trajectories for formation of the two diastereoisomers **3a** and **3b**.

A comparison of the possible transition states leading to the two diastereoisomers shows unfavorable steric interactions between the hydrogen at C-4 of the lactone pointing towards the nitrone and the *N*-phenyl group of nitrone in the *exo*-C=O TS (Scheme 2). The attack to the opposite face of lactone places the C=O group in the *endo* position, removing the strongest steric repulsions. Moreover, in the *endo*-C=O TS the carbonyl group, facing the *N*-phenyl, is settled for a stabilizing secondary orbital interaction [1a], which might work together steric effects in determining the high stereoselectivity. In order to give stronger support to this hypothesis and make the working effects clear, theoretical calcu-

lations of the two transition state structures have been performed [13]. The calculations gave a much higher energy for the *exo* TS (Figure 1), according to our proposed model and in good qualitative agreement with the observed diastereomeric ratio. The difference in energy must be ascribed essentially to steric effects, no favorable orbital overlapping being apparent. On the basis of these considerations, we speculated that the *endo*-C=O TS is favored and consequently we assigned the structure **3a**, with the *cis* relationship between C=O and the hydrogen at C-3' of the isoxazolidine ring, to the major product of the reaction. The minor diastereoisomer would then be **3b**, having the opposite relative stereochemistry at C-3' and C-5' of the isoxazolidine, derived from the *exo*-C=O TS. Thus, the major product of the cycloaddition of lactone **2** with the acyclic nitrone **1** would possess the opposite relative stereochemistry with respect to the cycloadduct from the same lactone with the cyclic nitrone [7]. However, this is only a consequence of the opposite stereochemistry at the C=N double bond of the reacting nitrone, the *endo* placement for C=O of the lactone being preferred in any case.

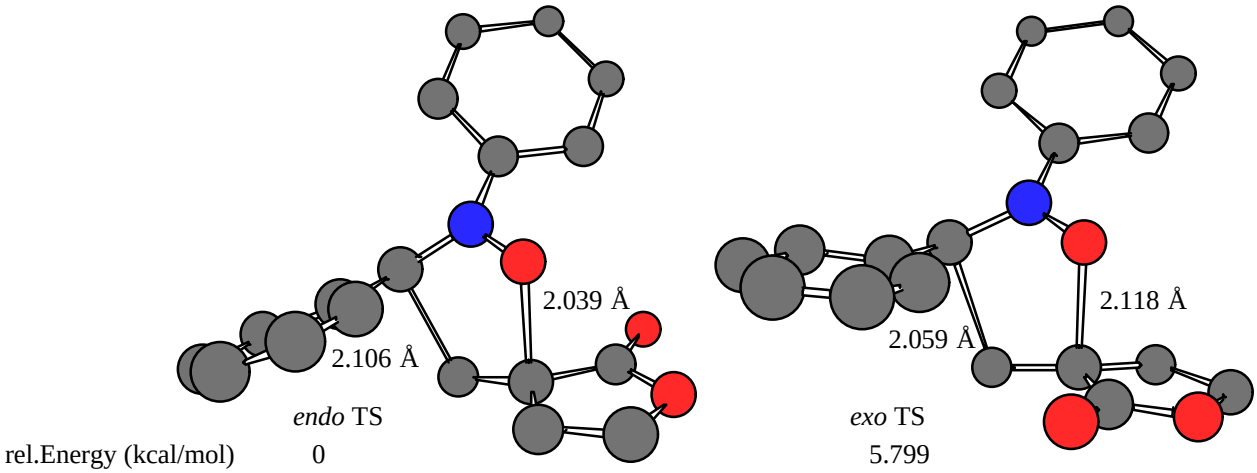


Figure 1. Calculated transition states from nitrone *Z*-**1** (hydrogen atoms are omitted).

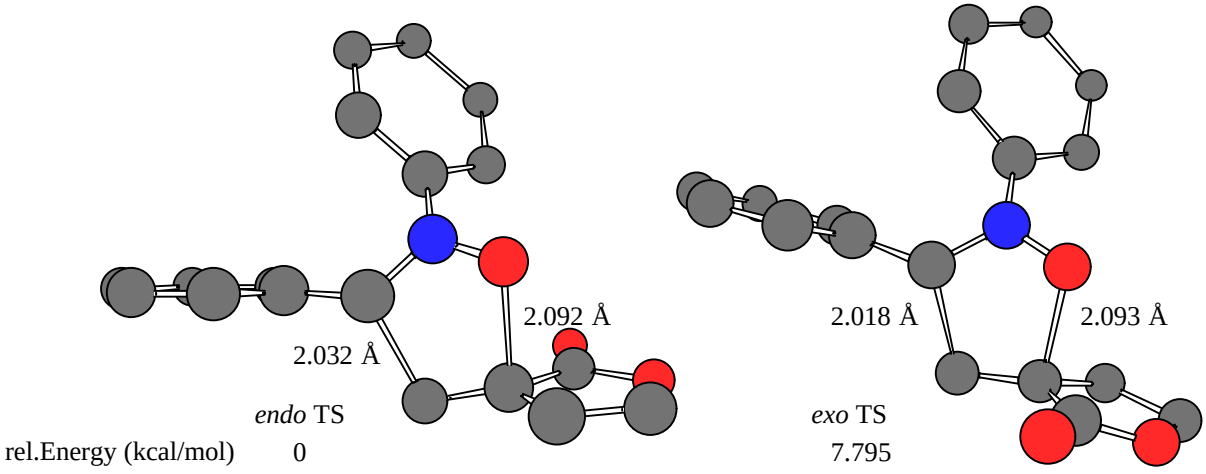


Figure 2. Calculated transition states from nitrone *E*-**1** (hydrogen atoms are omitted).

However, occurrence of cycloaddition through the less stable *E* isomer can not be ruled out. Similar calculations of TS from the *E*-nitrone showed the opposite preference for diastereoisomer **3b**, the alternate TS being even more differentiated in energy, still in favor of the *endo* approach (Figure 2).

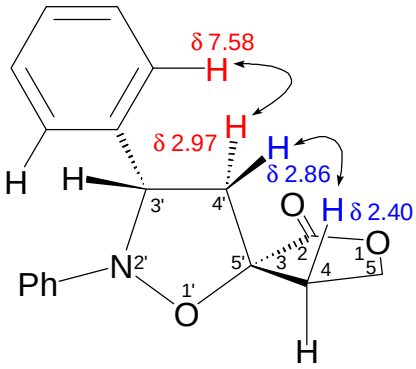


Figure 3. NOESY correlations for the minor isomer **3b**.

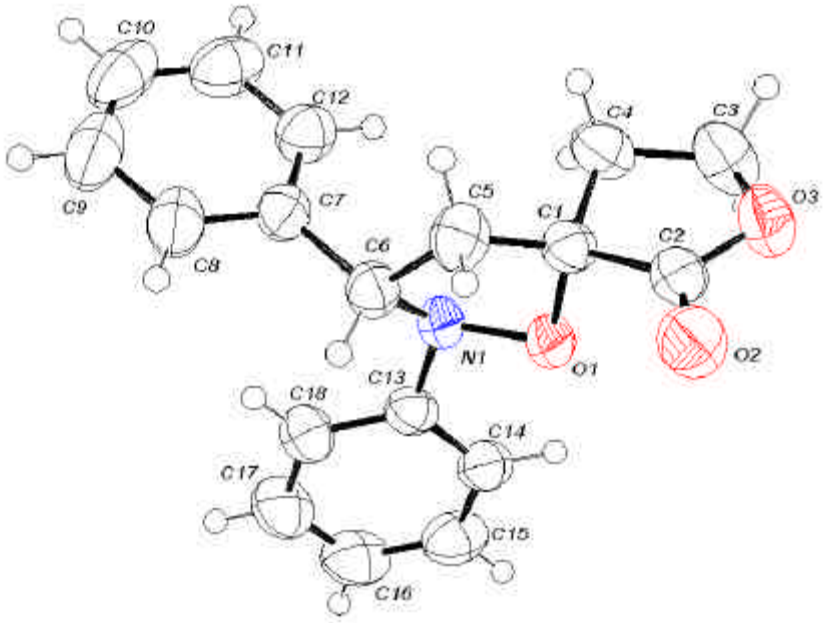


Figure 4. ORTEP view of the major isomer **3a**.

In search for an experimental support to our structural assignment, NOESY spectra of the two products were carried out in order to establish any effective correlation among protons. While no significant interaction was evidenced in the NOESY spectrum of **3a**, the spectrum of the minor isomer **3b** showed a correlation between the proton at C-4' of the isoxazolidine *trans* to the *C*-phenyl (δ 2.86 ppm) and a proton at C-4 of the lactone ring (Figure 3), which confirmed our assignment. The signal at δ 2.86 ppm was attributed to the C-4' proton *trans* to phenyl on the basis of a strong NOE interaction

between the ortho hydrogens of the C-phenyl group and its C-4' geminal proton (δ 2.97 ppm), which is therefore *cis* to phenyl (Figure 3). Definite assessment of the structural assignment as in Scheme 1 derived from an X-ray diffraction study performed on a single crystal of the major isomer **3a**, obtained by crystallization from methanol (Figure 4).

As far as acyclic nitrones are involved in cycloaddition reactions, an issue which is rarely taken into account is the stereoisomerism of the reacting nitrone. At the best, the same configuration of the more stable isomer is considered the reacting one as a preliminary unproven assumption. Comparison of the stereoselection data from the reported cycloaddition with the calculations performed on the corresponding transition states allows us to state that the reaction occurs, at least predominantly, from the more stable *Z* form of the nitrone. The major isomer is formed through the *exo*-C=O transition state, while the minor might derive either from the alternate *endo*-C=O TS or through the less stable *E* nitrone.

Conclusion

The results of cycloaddition reactions of methylenebutyrolactones with *C,N*-diphenylnitrone as a model acyclic nitrone have been reported. The reaction with α-methylene-γ-butyrolactone at 80°C showed a good 9:1 diastereoselectivity, which has been rationalized in terms of unfavorable steric effects at the transition state leading to the minor isomer, as evidenced by calculations.

Experimental

General

Methylenebutyrolactones **2** and **4** were obtained from Aldrich Chemical Company (USA) and were used as received. *C,N*-Diphenylnitrone (**1**) was synthesized as reported by condensation of benzaldehyde with phenylhydroxylamine [1d].

Melting points (mp) were measured with a Büchi 510 apparatus and are uncorrected. R_f values are referred to TLC on 0.25 mm silica gel plates (Merck F_{254}) by eluting with the same eluent used for the chromatographic separation of the compound. ^{1}H NMR spectra (in $CDCl_3$ solutions) were obtained using a Varian VXR 300 or a Bruker DRX 500 spectrometer and were recorded at 300 MHz and 500 MHz, respectively. ^{13}C NMR spectra (in $CDCl_3$ solutions) were obtained using a Varian Gemini 200 NMR and were recorded at 50 MHz. NMR signal assignments of proton signals were also allowed by bidimensional spectroscopy (COSY, NOESY) experiments. IR spectra were recorded with a Perkin Elmer 881. Mass spectra were measured with a QMD 1000 Carlo Erba Instrument (EI, 70 eV). Elemental analyses were recorded with a Perkin-Elmer 240 C instrument.

*Cycloaddition of C,N-Diphenylnitrone (**1**) to α-Methylene-γ-butyrolactone (**2**) at 80°C*

C,N-Diphenylnitrone (**1**, 394 mg, 2 mmol) was dissolved in benzene (3 mL) into a 10 mL round-

bottomed flask and α-methylene-γ-butyrolactone (**2**, 175 μL, 2 mmol) was added by a syringe. The solution was refluxed under a nitrogen atmosphere with magnetic stirring for 5 h, until the starting reagents were no more detected at a TLC control (dichloromethane as eluent). On concentration under vacuum, the resulting reaction mixture gave a yellowish solid, which was constituted by a 9:1 mixture of the two diastereoisomers **3a** and **3b**, as judged by integration of isolated signals in the ^{1}H NMR spectrum of the crude recorded at 500 MHz.

*Cycloaddition of C,N-Diphenylnitrone (**1**) to α-Methylene-γ-butyrolactone (**2**) at 110°C*

C,N-Diphenylnitrone (**1**, 302 mg, 1.53 mmol) was dissolved in toluene (3 mL) into a 10 mL round-bottomed flask and α-methylene-γ-butyrolactone (**2**, 135 μL, 1.53 mmol) was added by a syringe. The solution was refluxed under a nitrogen atmosphere with magnetic stirring for 3 h. On concentration under vacuum, the resulting reaction mixture gave a yellowish solid (403 mg, 89%), which was constituted by a 4:1 mixture of the two diastereoisomers **3a** and **3b** (500 MHz ^{1}H NMR). Partial dissolution of the mixture with toluene afforded a colorless precipitate, which was filtered, washed with diisopropylether and dried. The solid resulted the pure major isomer **3a** (272 mg, 0.92 mmol, 60%) from a ^{1}H NMR analysis. The organic solution was concentrated to give a mixture of **3a** and **3b** (131 mg) enriched in the minor isomer, which was separated by flash column chromatography, eluent CH_2Cl_2/petroleum ether/*n*-BuOH 50:50:1. Three fractions were collected, the first containing the pure major isomer **3a** (R_f 0.18, 10 mg, 0.03 mmol, 2%), the intermediate containing a mixture of the two diastereoisomers (70 mg, 15%), and the last one containing the pure minor isomer **3b** (R_f 0.12, 39 mg, 0.13 mmol, 9%) as a colorless solid.

Data of (3S,3'R*)-Spiro[tetrahydrofuran-2-one-3,5'-(2',3'-diphenyl)tetrahydroisoxazole] (**3a**)*

Mp 125-126°C (*i*Pr_2O).

^{1}H NMR (300 MHz) δ: 7.53-7.49 (m, 2 H, C-Ph), 7.43-7.33 (m, 3 H, C-Ph), 7.24-7.18 (m, 2 H, N-Ph), 7.03-6.95 (m, 3 H, N-Ph), 5.02 (apparent t, J = 7.5 Hz, 1 H, C3'-H), 4.48 (ddd, J = 9.1, 8.3, 6.8 Hz, 1 H, C5-H), 4.32 (ddd, J = 9.1, 8.2, 3.8 Hz, 1 H, C5-H), 3.12 (dd, J = 12.6, 7.4 Hz, 1 H, C4'-H), 2.61 (ddd, J = 13.8, 6.8, 3.8 Hz, 1 H, C4-H), 2.56 (dd, J = 12.6, 7.6 Hz, 1 H, C4'-H), 2.33 (dt, J = 13.8, 8.2 Hz, 1 H, C4-H).

^{13}C NMR δ: 174.8 (s, C2), 150.3 (s, N-C_{ipso}Ph), 139.8 (s, C-C_{ipso}Ph), 128.8 (d, 2 C, C-Ph), 128.4 (d, 2 C, C-Ph), 127.7 (d, C-Ph), 126.6 (d, 2 C, N-Ph), 122.9 (d, N-Ph), 116.3 (d, 2 C, N-Ph), 81.2 (s, C3), 70.1 (d, C3'), 65.6 (t, C5), 46.1 (t, C4'), 34.1 (t, C4).

IR (KBr) cm^{-1}: 3063, 2987, 1781, 1596, 1486, 1245, 1184, 1021.

MS *m/z* (%): 295 (M^+, 25), 194 (31), 180 (47), 143 (30), 128 (38), 104 (42), 91 (100), 77 (88).

Anal. Calcd for $C_{18}H_{17}NO_3$: C 73.20, H 5.80, N 4.74; found: C 73.50, H 5.75, N 4.90.

Data of (3S,3'S*)- Spiro[tetrahydrofuran-2-one-3,5'-(2',3'-diphenyl)tetrahydroisoxazole] (***3b***)*

Mp 127-128°C (*i*Pr_2O).

^{1}H NMR (500 MHz) δ: 7.60-7.56 (m, 2 H, C-Ph), 7.42-7.37 (m, 2 H, C-Ph), 7.36-7.31 (m, 1 H, C-Ph), 7.22-7.16 (m, 2 H, N-Ph), 7.01-6.94 (m, 3 H, N-Ph), 4.56 (dd, J = 9.1, 7.8 Hz, 1 H, C3'-H), 4.51 (ddd, J = 9.1, 7.5, 7.0 Hz, 1 H, C5-H), 4.36 (ddd, J = 9.1, 7.8, 4.5 Hz, 1 H, C5-H), 2.97 (dd, J = 12.6, 9.1 Hz, 1 H, C4'-H), 2.86 (dd, J = 12.6, 7.8 Hz, 1 H, C4'-H), 2.61 (ddd, J = 13.6, 6.9, 4.5 Hz, 1 H, C4-H), 2.40 (dt, J = 13.6, 7.7 Hz, 1 H, C4-H).

^{13}C NMR δ: 174.3 (s, C2), 149.8 (s, N-C_{ipso}Ph), 139.3 (s, C-C_{ipso}Ph), 128.9 (d, 2 C, C-Ph), 128.5 (d, 2 C, C-Ph), 128.0 (d, C-Ph), 127.3 (d, 2 C, N-Ph), 123.0 (d, N-Ph), 116.7 (d, 2 C, N-Ph), 80.6 (s, C3), 69.9 (d, C3'), 65.3 (t, C5), 47.0 (t, C4'), 34.6 (t, C4).

IR (KBr) cm^{-1}: 3063, 2916, 1774, 1597, 1486, 1242, 1187, 1014.

MS *m/z* (%): 295 (M^+, 16), 194 (29), 180 (41), 143 (29), 128 (40), 104 (38), 91 (75), 77 (100).

Anal. Calcd for $C_{18}H_{17}NO_3$: C 73.20, H 5.80, N 4.74; found: C 73.17, H 5.90, N 4.69.

X-Ray Structural Analysis of (3S,3'R*)-Spiro[tetrahydrofuran-2-one-3,5'-(2',3'-diphenyl)tetrahydroisoxazole] (***3a***)*

$C_{18}H_{17}NO_3$, M=295.33, triclinic, space group P-1, *a*=8.847(5) Å, *b*=9.024(5) Å, *c*=10.713(5) Å, α=109.670(5)°, β=92.780(5)°, γ=108.370(5)°, V=752.8(7) $Å^3$, Z=2 D_c=1.303, μ=0.721 mm^{-1}, F(000)=312.

Analysis on prismatic colorless single crystal was carried out with a Siemens P4 X-ray diffractometer at room temperature. Graphite-monochromated Cu Kα radiation was used for cell parameter determination and data collection. The intensities of two standard reflections were monitored during data collection to check the stability of the crystal: no loss of intensity was recognized. The integrated intensities, measured using the θ/2θ scan mode, were corrected for Lorentz and polarization effects [14]. The reflections collected were 2605 with a 4.45<θ< 59.97 range; 2147 were indipendent and the final R index was 0.0414 for reflections having I>2σI, and 0.0435 for all data. The non-hydrogen atoms were refined anisotropically; aromatic hydrogens were assigned in calculated positions and the others were found in the Fourier difference synthesis; all of them were refined as isotropic. This structure was solved by direct methods of SIR92 [15] and refined using the full-matrix least squares on F^2 provided by SHELXL97 [16]. Crystallographic data for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre and allocated with the deposition number CCDC-140748. The found values for bond lengths and bond angles of **3a** are reported in Tables 1 and 2, respectively.

Table 1. Bond lengths [Å] for **3a**.

O(1)-C(1)	1.435(2)	C(3)-H(3A)	0.99(3)	C(8)-C(9)	1.388(3)	C(14)-C(15)	1.384(2)
O(1)-N(1)	1.464(2)	C(3)-H(3B)	1.02(3)	C(8)-H(8)	0.93	C(14)-H(14)	0.93
O(2)-C(2)	1.194(2)	C(4)-H(4A)	0.97(2)	C(9)-C(10)	1.370(4)	C(15)-C(16)	1.379(3)
O(3)-C(2)	1.335(2)	C(4)-H(4B)	0.97(2)	C(9)-H(9)	0.93	C(15)-H(15)	0.93
O(3)-C(3)	1.462(3)	C(5)-C(6)	1.544(2)	C(10)-C(11)	1.377(4)	C(16)-C(17)	1.376(3)
N(1)-C(13)	1.420(2)	C(5)-H(5A)	0.96(2)	C(10)-H(10)	0.93	C(16)-H(16)	0.93
N(1)-C(6)	1.489(2)	C(5)-H(5B)	0.95(2)	C(11)-C(12)	1.385(3)	C(17)-C(18)	1.385(3)
C(1)-C(5)	1.513(2)	C(6)-C(7)	1.518(2)	C(11)-H(11)	0.93	C(17)-H(17)	0.93
C(1)-C(4)	1.513(2)	C(6)-H(6)	0.94(2)	C(12)-H(12)	0.93	C(18)-H(18)	0.93
C(1)-C(2)	1.535(2)	C(7)-C(8)	1.383(2)	C(13)-C(18)	1.391(2)		
C(3)-C(4)	1.509(3)	C(7)-C(12)	1.384(3)	C(13)-C(14)	1.392(2)		

Table 2. Angles [deg] for **3a**.

C(1)-O(1)-N(1)	102.12(10)	H(4A)-C(4)-H(4B)	110(2)	C(10)-C(11)-C(12)	120.2(2)
C(2)-O(3)-C(3)	110.83(14)	C(1)-C(5)-C(6)	104.52(14)	C(10)-C(11)-H(11)	119.88(13)
C(13)-N(1)-O(1)	108.46(11)	C(1)-C(5)-H(5A)	112.4(13)	C(12)-C(11)-H(11)	119.88(14)
C(13)-N(1)-C(6)	118.77(12)	C(6)-C(5)-H(5A)	113.0(12)	C(7)-C(12)-C(11)	120.4(2)
O(1)-N(1)-C(6)	105.18(11)	C(1)-C(5)-H(5B)	109.6(12)	C(7)-C(12)-H(12)	119.78(11)
O(1)-C(1)-C(5)	103.40(13)	C(6)-C(5)-H(5B)	108.3(13)	C(11)-C(12)-H(12)	119.78(14)
O(1)-C(1)-C(4)	111.98(14)	H(5A)-C(5)-H(5B)	109(2)	C(18)-C(13)-C(14)	119.1(2)
C(5)-C(1)-C(4)	118.1(2)	N(1)-C(6)-C(7)	110.89(13)	C(18)-C(13)-N(1)	120.5(2)
O(1)-C(1)-C(2)	104.04(12)	N(1)-C(6)-C(5)	102.86(13)	C(14)-C(13)-N(1)	120.12(14)
C(5)-C(1)-C(2)	115.82(14)	C(7)-C(6)-C(5)	114.07(14)	C(15)-C(14)-C(13)	119.9(2)
C(4)-C(1)-C(2)	102.92(13)	N(1)-C(6)-H(6)	111.0(11)	C(15)-C(14)-H(14)	120.03(12)
O(2)-C(2)-O(3)	122.1(2)	C(7)-C(6)-H(6)	108.7(11)	C(13)-C(14)-H(14)	120.03(9)
O(2)-C(2)-C(1)	127.6(2)	C(5)-C(6)-H(6)	109.3(11)	C(16)-C(15)-C(14)	120.8(2)
O(3)-C(2)-C(1)	110.3(2)	C(8)-C(7)-C(12)	118.9(2)	C(16)-C(15)-H(15)	119.58(12)
O(3)-C(3)-C(4)	105.7(2)	C(8)-C(7)-C(6)	118.9(2)	C(14)-C(15)-H(15)	119.58(11)
O(3)-C(3)-H(3A)	105.8(14)	C(12)-C(7)-C(6)	122.1(2)	C(17)-C(16)-C(15)	119.3(2)
C(4)-C(3)-H(3A)	115.1(14)	C(7)-C(8)-C(9)	120.4(2)	C(17)-C(16)-H(16)	120.34(11)
O(3)-C(3)-H(3B)	104(2)	C(7)-C(8)-H(8)	119.82(11)	C(15)-C(16)-H(16)	120.34(12)
C(4)-C(3)-H(3B)	111.5(14)	C(9)-C(8)-H(8)	119.8(2)	C(16)-C(17)-C(18)	120.7(2)
H(3A)-C(3)-H(3B)	113(2)	C(10)-C(9)-C(8)	120.3(2)	C(16)-C(17)-H(17)	119.64(11)
C(3)-C(4)-C(1)	104.4(2)	C(10)-C(9)-H(9)	119.84(13)	C(18)-C(17)-H(17)	119.64(12)
C(3)-C(4)-H(4A)	111.6(12)	C(8)-C(9)-H(9)	119.84(14)	C(17)-C(18)-C(13)	120.1(2)
C(1)-C(4)-H(4A)	109.2(12)	C(9)-C(10)-C(11)	119.7(2)	C(17)-C(18)-H(18)	119.95(12)
C(3)-C(4)-H(4B)	112.6(13)	C(9)-C(10)-H(10)	120.13(13)	C(13)-C(18)-H(18)	119.95(10)
C(1)-C(4)-H(4B)	109.1(12)	C(11)-C(10)-H(10)	120.13(13)		

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Samples Availability: Available from the authors.