Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

1,3-Dipolar Cycloaddition of Nitrones with 5-Methylenehydantoins: Synthesis and Transformation of New Spirohydantoin Derivatives

Amira Bahy [a], Yakdhane Kacem [a] & Béchir Ben Hassine [a]

[a] Laboratory of Asymmetric Organic Synthesis and Homogeneous Catalysis, Faculty of Sciences , Monastir, Tunisia

Published online: 07 Apr 2010.

To cite this article: Amira Bahy , Yakdhane Kacem & Béchir Ben Hassine (2010) 1,3-Dipolar Cycloaddition of Nitrones with 5-Methylenehydantoins: Synthesis and Transformation of New Spirohydantoin Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:9, 1377-1390, DOI: 10.1080/00397910903097237

To link to this article: http://dx.doi.org/10.1080/00397910903097237

Synthetic Communications®, 40: 1377–1390, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903097237

Taylor & Francis
Taylor & Francis Group

1,3-DIPOLAR CYCLOADDITION OF NITRONES WITH 5-METHYLENEHYDANTOINS: SYNTHESIS AND TRANSFORMATION OF NEW SPIROHYDANTOIN DERIVATIVES

Amira Bahy, Yakdhane Kacem, and Béchir Ben Hassine
Laboratory of Asymmetric Organic Synthesis and Homogeneous Catalysis, Faculty of Sciences, Monastir, Tunisia

1,3-Dipolar cycloaddition of various acyclic nitrones with 5-methylenehydantoin derivatives afforded new chiral spiroadducts in good yields. All the spirohydantoins were obtained through a regio- and stereospecific pathway, and the spirocarbon atom was linked to the isoxazolidine oxygen atom. A representative example of the reduction of the spirohydantoin 8 with Zn/AcOH led to the substituted 1,3-aminoalcohol hydantoin 20.

Keywords: 1,3-Dipolar cycloaddition; 5-methylenehydantoins; nitrones; regioselectivity; stereoselectivity

INTRODUCTION

1,3-Dipolar cycloaddition reactions are the most important and versatile methods to build five-membered heterocycles.[1–5] They have been applied to the synthesis of natural products such as sugar derivatives,[6] β-lactams,[7] amino acids,[8] and alkaloids.[9]

Several examples of naturally occurring and synthetic hydantoin[10] and spirohydantoin derivatives[11,12] undergo 1,3-dipolar cycloaddition to give numerous compounds that exhibit various biological activities, such as antitumor,[13] anti-arrhythmic,[14] anticonvulsant,[15] neurotransmissive,[16] herbicidal,[17] and cytotoxic activities,[18] and act as inhibitors of glycogen phosphorylase[19] and aldose reductase.[20] Among these biologically active compounds are hydantocidin (**I**) and its analogs,[17–20] tetrantoin (**II**),[15] and spiro[(dihydroimidazo-2,4-dione)-5,3′-(2′,3′-dihydrothieno[2,3-*b*]naphtho-4′,9′-dione)] derivatives (**III**)[18] (Fig. 1).

In this work, we report the synthesis of the new spirohydantoin derivatives **8–19** and their reduction with Zn/AcOH. Our synthetic strategy is based on the use of a methylenehydantoin derivative as the starting material to prepare spirohydantoins, via 1,3-dipolar cycloaddition.

Received February 7, 2009.

Address correspondence to Béchir Ben Hassine, Laboratoire de Synthèse Organique Asymétrique et Catalyse Homogène (O1UR1201), Faculté des Sciences, Avenue de l'environnement, 5019 Monastir, Tunisia. E-mail: bechirbenhassine@yahoo.fr

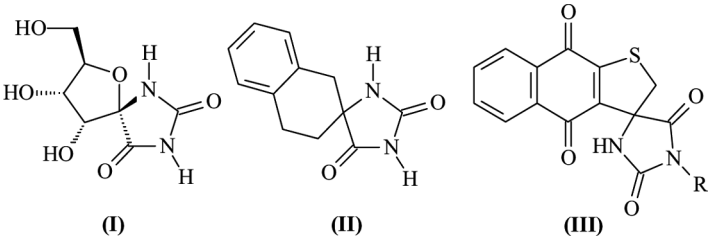


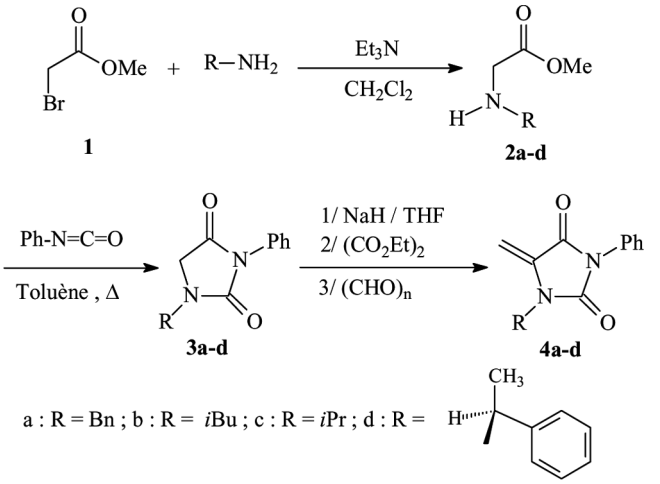
Figure 1. Hydantoin derivatives exhibiting biological activities.

RESULTS AND DISCUSSION

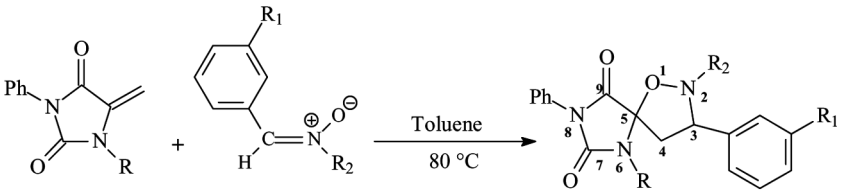
The starting compounds 5-methylenehydantoins **4a–d** were prepared from α-bromomethylester **1** according to Scheme 1. Treatment of various primary amines with compound **1** gives produced the corresponding α-aminomethylester derivatives **2a–d** in 50 to 70% yields. Derivatives **2a–d**[21] were then treated with phenylisocyanate in refluxing toluene to furnish the *N,N′*-diprotected hydantoins **3a–d**[22] in 50 to 90% yields. Finally, the desired new *N,N′*-diprotected 5-methylenehydantoins **4a–d** were prepared in good yield according to the published procedure.[23]

The initial investigation on the 1,3-dipolar cycloaddition of 5-methylenehydantoins **4a–d** with nitrones **5–7** involved the study of the reaction of **4a** with nitrone **5** at 110 °C in toluene solution for 24 h; compound **8** was obtained in 20% yield. Heating the same mixture at 80 °C for 24 h generated the product **8** in only 35% yield. Finally, the reaction of **4a** with **5** in toluene at 80 °C for 6 days produced **8** in 63%. Increase in reactional time beyond 6 days (up to 10 days) has not shown a variation in the output.

In the light of these results, we decided to perform all cycloaddition reactions of dipolarophiles **4a–d** with nitrones **5–7** at 80 °C in a diluted toluene solution (0.02 M) for 6 days (Scheme 2). Yields of **8–19** range between 50 and 74% (Table 1).



Scheme 1. Synthesis of methylenehydantoins.



4a-d **5-7** **8-19**

5 : $R_1 = H$; $R_2 = Ph$; **6 :** $R_1 = H$; $R_2 = t\text{-Bu}$; **7 :** $R_1 = OCH_3$; $R_2 = i\text{-Pr}$

Scheme 2. Reaction of methylenehydantoins with nitrones and reaction conditions.

Regiochemistry and Stereochemistry

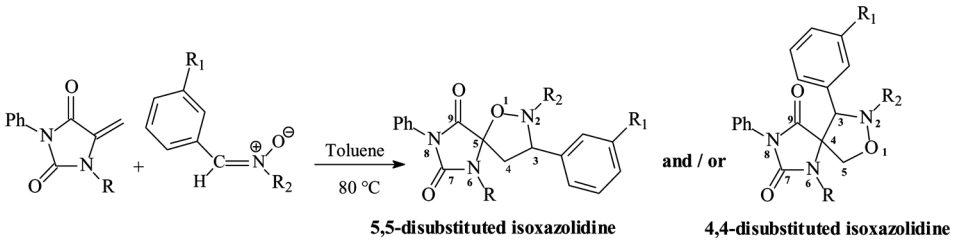
Two possible regioisomers of the cycloadduct can be theoretically obtained: the 5,5-disubstituted isoxazolidine and/or the 4,4-disubstituted isoxazolidine (Scheme 3). In practice, we have obtained only one product. The structure of each cycloadduct was confirmed by NMR (^1H and ^{13}C) spectra of the crude cycloaddition reaction mixtures. Comparison of the ^{13}C NMR data of spiroadducts **8–19** suggests that these compounds possess the same regiochemistry. The spirocarbon resonance of all adducts was between 90 and 93 ppm; this value located the spiro center near the very electronegative oxygen atom of the isoxazolidine ring.

In addition, the ^1H NMR analysis clearly indicated that all spiroadducts were 5,5-disubstituted isoxazolidine regioisomers; the signal of proton 3-H appeared as a triplet or a doublet of doublets around $\delta = 3.98$–4.94 ppm. It is coupled with protons 4-H and 4′-H. This excluded the presence of the inverse regioisomer (4,4-disubstituted isoxazolidine), in which the NMR spectrum would exhibit a singlet for 3-H and an AB system for the two hydrogen atoms at the 5-position of the isoxazolidine ring. These results also supported the literature reports.[24–27] The configuration of the cycloadduct **15** was established by x-ray crystallography as (3R5R, 3S5S): this

Table 1. Yields of adducts

Entry	Methylenehydantoin	Nitrone	Adducts[a,b]	Yield (%)
1	4a	5	8	63
2	4a	6	9	71
3	4a	7	10	55
4	4b	5	11	60
5	4b	6	12	58
6	4b	7	13	50
7	4c	5	14	70
8	4c	6	15	60
9	4c	7	16	60
10	4d	5	17	70
11	4d	6	18	52
12	4d	7	19	74

[a]Reaction in toluene at 80 °C for 6 days.
[b]Yield of pure **8–19**.



Scheme 3. Regiochemistry of cycloaddition.

analysis proves that we obtain only the 5,5-disubstituted regioisomer (Fig. 2), which resulted from the endo approach of the dipole toward the hydantoin carbonyl group. The examination of this structure revealed a *cis* relationship between the proton 3-H and the C=O group of the hydantoin ring.

The cycloaddition of 5-methylenehydantoins with nitrones led to cycloadducts having two new chiral centers: the quaternary spiroatom and the carbon linked to the substituted phenyl group of the isoxazolidine ring.

The formation of diastereoisomeric adducts was never caused by any Z/E interconversion of nitrons,[26–28] the relative configuration (Z) of the dipole being always preserved in spirocompounds. Indeed, the high-performance liquid chromatographic (HPLC) analysis of the crude cycloaddition reaction shows the formation of only one diastereoisomer for adducts **8–16**. Unlike cycloaddition of chiral methylenehydantoin **4d**, that with nitrones proceeded stereoselectively, and HPLC analysis shows the formation of two nonracemic diastereoisomers.

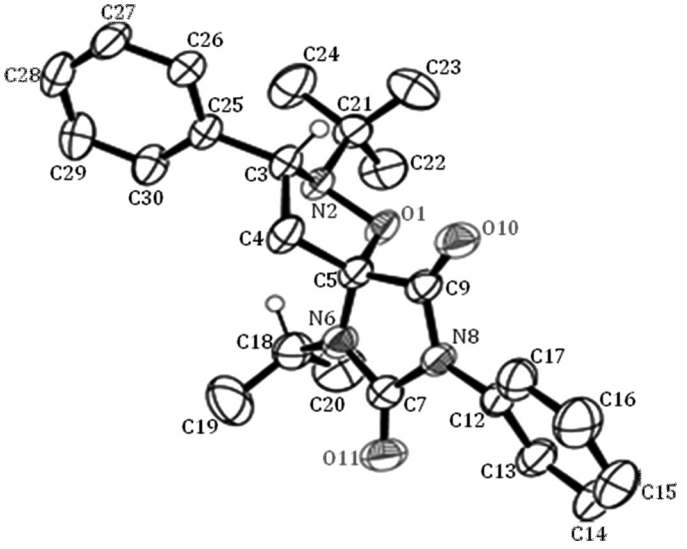
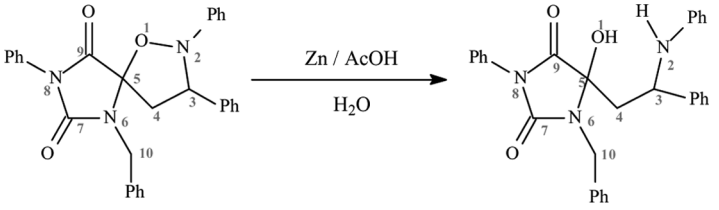


Figure 2. ORTEP view of adduct **15**.



Scheme 4. Reduction of spiroadduct **8**.

Reduction of Spiroadduct 8

The reduction of compound **8**[29] with zinc in acetic acid and water at 70 °C gave product **20,** obtained by a simple opening of the isoxazolidine ring (Scheme 4).

The spectroscopic data (^{1}H and ^{13}C NMR) were in good agreement with the assigned structure **20**. The difference between ^{13}C NMR spectrum of the compound **8** and that of compound **20** appears at the chemical shift of the quaternary carbon C5. Its chemical shift appears at 91 ppm in the spiranic form and at 66 ppm after the ring opening. ^{1}H NMR spectrum shows the presence of two new wide signals at 4.8 ppm corresponding to labile protons (OH and NH).

CONCLUSION

We have studied the reactivity of methylenehydantoins **4a**–**d** toward acyclic nitrones **5**–**7**. All spiroadducts were formed via a very high regioselectivity pathway, and the spirocarbon atom was linked to the isoxazolidine oxygen atom.

The continuous pharmaceutical interest in the spirohydantoin compounds[21] may justify further exploration of these results in the pharmacological field.

EXPERIMENTAL

General

All reactions were monitored on thin-layer chromatographic (TLC) Merck 60 F-254 silica-gel plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (70–230 mesh) using ethyl acetate and cyclohexane mixture as eluents. Melting points were determined on an Electrothermal 9002 apparatus and are uncorrected. The optical rotation was measured by Atago Polax-2 L polarimeter. NMR spectra were recorded on a Bruker AC 300 spectrometer [300 MHz (^{1}H) and 75 MHz (^{13}C)]. All chemical shifts were reported as δ values (ppm) relative to internal tetramethylsilane. Infrared (IR) spectra (KBr) were recorded on a Fourier transform (FT)–IR 8400 Shimadzu spectrophotometer. Mass spectra (MS) were recorded on a Hewlett-Packard (HP) 5792. High-resolution mass spectroscopy (HRMS) was carried on Micromass LCTKC420. A Jasco HPLC system provided with a Jasco 2080 pump, an automatic injector Rheodyne (7725 I), ultraviolet (UV) detector (Jasco 2075), and a system data processor weres used (Clarity Lite). The chromatographic analysis was performed on a C18 column (250 mm × 4.6 mm).

A mobile phase of methanol/hexane [80:20] was used with a flow rate of 0.6 mL/min. Detection was performed at 254 nm.

The crystal data for $C_{24}H_{29}N_3O_3$ were recorded on a Nonis MACH3/CAD4 diffractometer: M = 407.50, triclinic, P-1, a = 9.976(5) Å, b = 10.735(5) Å, c = 11.134(5) Å, V = 1129.1(9) Å^3, Z = 2, D_c = 1.199 mg/m^3, x-ray source Mo Kα (radiation), k = 0.71069 Å, F(000) = 436, T = 293(2) K, colorless plates 0.40 × 0.30 × 0.20 mm. The structure was worked out by direct methods and refined anisotropically using a full-matrix with least squares method based on F^2 to give R1 = 0.0565, wR2 = 0.1319 for 7593 independent observed reflections and 387 parameters. Crystallographic data (excluding structure factors) for the structure in this article have been deposited with the Cambridge Crystallographic Data Centre as a supplementary publication number CCDC 670177. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Methylenehydantoins **4**[23] and nitrones **5–7**[30–33] were prepared according to the literature procedures.

Synthesis of Methylenehydantoins

Preparation of the α-aminomethylester derivatives (2a–d). The primary amine (50 mmol) was dissolved in 10 mL of dichloromethane, and triethylamine (30 mmol) was added. The α-bromomethylester **1** (25 mmol) was added dropwise at 0 °C. Once the addition finished, the solution was stirred overnight at room temperature. The solution was acidified with HCl (2 M, 15 mL) and extracted three times with methylene chloride (3 20 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under a reduced pressure. The crude residue was purified by column chromatography [SiO_2–hexane/ethyl acetate (80:20)].

N-Benzylaminoester 2a. Yellow oil (50%); ^{1}H NMR (300 MHz, $CDCl_3$): 1.91 (s, NH), 3.36 (s, CH_2-CO), 3.66 (s, OCH_3), 3.74 (s, CH_2Bn), 7.19–7.27 (m, 5H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): 49.9 (CH_2-Bn), 51.8 (CH_2-CO), 53.3 (OCH_3), 127.2–139.4 (C_{arom}), 172.9 (COO); MS (IE): ($C_{10}H_{13}NO_2$): m/z = 179 [M^+], 120, 106, 91, 65.

N-Isobutylaminoester 2b. Yellow oil (63%); ^{1}H NMR (300 MHz, $CDCl_3$): 0.85 (d, 2CH_3-*i*Bu, J = 6.6 Hz), 1.61 (s, NH), 1.62–1.69 (m, CH-*i*Bu), 2.34 (d, CH_2-*i*Bu, J = 6.9 Hz), 3.34 (s, CH_2-CO), 3.66 (s, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.9 (2CH_3-*i*Bu), 28.8 (CH_2-*i*Bu), 51.3 (CH-*i*Bu), 52.1 (CH_2-CO), 58.0 (OCH_3), 173.4 (CO-O); MS(IE): ($C_7H_{15}NO_2$): m/z = 145 [M^+], 144, 116, 98, 86, 72, 55, 41.

N-Isopropylaminoester 2c. Yellow oil (55%); ^{1}H NMR (300 MHz, $CDCl_3$): 0.99 (d, 2CH_3-*i*Pr, J = 6.3 Hz), 1.73 (s, NH), 2.68–2.77 (m, CH-*i*Pr), 3.35 (s, CH_2-CO), 3.66 (s, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): 23.0 (2CH_3-*i*Pr), 48.6 (CH_2-CO), 48.8 (CH-*i*Pr), 52.1 (OCH_3), 173.4 (COO); MS (IE): ($C_6H_{13}NO_2$): m/z = 131 [M^+], 130, 116, 91, 88, 56, 43.

N-[(1S)-1-Phenylethyl]aminoester 2d. Yellow oil (60%); $[\alpha]_D^{17} + 0.9$ (c = 3.33, AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$): 1.39 (d, CH_3, J = 6.6 Hz), 1.95 (s, NH), 3.28 (d, CH_2-CO, J = 6.9 Hz), 3.69 (s, OCH_3), 3.79 (q, CH), 2.68–2.77 (m,

$5H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 24.69 (CH_3), 49.0 (CH), 52.1 (CH_2-CO), 58.1 (OCH_3), 127.1–144.9 (C_{arom}), 173.4 (COO).

Preparation of hydantoins (3a–d). In a 100-mL, round-bottomed flask fitted with a magnetic stirrer, 10 mmol of α-aminomethylester, 10 mmol of phenylisocyanate, and 10 mL of anhydrous toluene were placed. The resulting mixture was stirred and heated to reflux under an argon atmosphere until complete consumption of the starting materials (TLC analysis). The reaction mixture was allowed to cool to room temperature and concentrate. The residue obtained was purified by column chromatography [SiO_2–cyclohexane/ethyl acetate (90:10)].

1-Benzyl-3-phenylimidazolidine-2,4-dione 3a. White solid (90%); mp = 141–143 °C (ethyl acetate/hexane); ^1H NMR (300 MHz, $CDCl_3$): 3.76 (s, CH_2-Bn), 4.18 (s, CH-CO), 4.65 (s, CH-CO), 7.01–7.45 (m, $10H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 50.0 (CH_2-Bn), 52.8 (CH_2-CO), 120.2–139.0 (C_{arom}), 156.3 (NCON), 171.3 (CO); MS (IE): ($C_{16}H_{14}N_2O_2$): $m/z = 266$ [M^+], 223, 175, 132, 119, 104, 91, 77, 65.

1-Isobutyl-3-phenylimidazolidine-2,4-dione 3b. White solid (50%); mp = 89–91 °C (ethyl acetate/hexane); ^1H NMR (300 MHz, $CDCl_3$): 0.99 (d, $2CH_3$-*i*Bu, $J = 6.6$ Hz), 1.95–2.00 (m, CH-*i*Bu), 3.28 (d, CH_2-*i*Bu, $J = 7.5$ Hz), 4.03 (s, CH_2-CO), 7.35–7.50 (m, $5H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.3 ($2CH_3$-*i*Bu), 27.6 (CH_2-*i*Bu), 50.5 (CH-*i*Bu), 50.9 (C_5), 126.4–132.1 (C_{arom}), 156.2 (NCON), 169.3 (CO); MS (IE): ($C_{13}H_{16}N_2O_2$): $m/z = 232$ [M^+], 189, 176, 119, 91, 42.

1-Isopropyl-3-phenylimidazolidine-2,4-dione 3c. White solid (60%); mp = 69–71 °C (ethyl acetate/hexane); ^1H NMR (300 MHz, $CDCl_3$): 1.22 (d, $2CH_3$-*i*Pr, $J = 6.9$ Hz), 3.92 (s, CH_2-CO), 4.41–4.47 (m, CH-*i*Pr), 7.31–7.46 (m, $5H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.1 ($2CH_3$-*i*Pr), 43.6 (CH-*i*Pr), 45.0 (C5), 126.1–131.8 (C_{arom}), 154.8 (NCON), 169.2 (CO); MS (IE): ($C_{12}H_{14}N_2O_2$): $m/z = 218$ [M^+], 203, 119, 91, 77, 56, 41.

3-Phenyl-1-[(1S)-1-phenylethyl]imidazolidine-2,4-dione 3d. Previously reported.[22] Yellow oil (75%); $[\alpha]_D^{17} + 0.9$ (c = 3.15, AcOEt); ^1H NMR (300 MHz, $CDCl_3$): 1.21 (d, CH_3, $J = 7.2$ Hz), 3.66 (d, CH_2-CO, $J = 17.4$ Hz), 3.96 (d, CH_2-CO, $J = 17.4$ Hz), 3.60 (q, CH), 7.28–7.51 (m, $10H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 17.27 (CH_3), 45.9 (CH_2-CO), 50.6 (CH), 126.4–139.5 (C_{arom}), 155.5 (NCON), 169.3 (CO).

Preparation of methylenehydantoins (4a–d). Sodium hydride (60% dispersion in mineral oil, 5.16 mmol, 1.29 eq.) and diethyl oxalate (6 mmol, 1.5 eq.) were suspended in anhydrous tetrahydrofrun (THF, 5 mL), and the mixture was heated to 60 °C under an argon atmosphere. The appropriate hydantoin (4 mmol, 1 eq.) was added dropwise. The resulting mixture was stirred and heated to 60 °C under an argon atmosphere for 48 h, cooled, and dried under reduced pressure. The resulting sodium salt of the 3-ethoxalylhydantoin and paraformaldehyde (8 mmol, 2 eq.) was then suspended in xylene (10 mL), and the heterogeneous mixture was stirred to reflux for 2 h. After cooling to room temperature, the solid residue was filtered and washed with xylene. The filtrates were evaporated under a reduced

pressure, and the corresponding residue was purified by column chromatography [SiO_2–cyclohexane/ethyl acetate (90:10)].

1-Benzyl-5-methylene-3-phenylimidazolidine-2,4-dione 4a. Previously reported.[5] White solid (80%); mp = 104–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 4.73 (d, CH_2=C, J = 2.4 Hz), 4.80 (s, CH_2-Bn), 5.40 (d, CH_2=C, J = 2.4 Hz), 7.18–7.42 (m, 10H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): 44.8 (CH_2-Bn), 96.5 (CH_2=C), 126.0–135.2 (C_{arom}), 135.5 (C_q=C), 153.7 (NCON), 161.7 (CO); IR (KBr)/cm^{-1}: $\nu_{C\text{-}N}$ = 1419, $\nu_{C=Carom}$ = 1493, $\nu_{C=CH2}$ = 1656, $\nu_{C=O}$ = 1729, $\nu_{C=O}$ = 1777, $\nu_{C\text{-}Harom}$ = 3059; MS (IE): ($C_{17}H_{14}N_2O_2$): m/z = 278 [M$^+$], 131, 119, 103, 91, 77, 65, 51.

1-Isobutyl-5-methylene-3-phenylimidazolidine-2,4-dione 4b. White solid (50%); mp = 71–73 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 0.98 (d, 2CH_3-*i*Bu, J = 6.6 Hz), 2.08–2.17 (m, CH-*i*Bu), 3.47–3.50 (d, CH_2-*i*Bu, J = 7.5 Hz), 4.86 (d, CH_2=C, J = 2.1 Hz), 5.52 (d, CH_2=C, J = 2.1 Hz), 7.35–7.50 (m, 5H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.1 (2CH_3-*i*Bu), 27.0 (CH-*i*Bu), 48.1 (CH_2-*i*Bu), 95.0 (CH_2=C), 125.9–131.4 (C_{arom}), 135.9 (C_q=C), 153.4 (NCON), 161.5 (CO); MS (IE): ($C_{14}H_{16}N_2O_2$): m/z = 244 [M$^+$], 201, 188, 119, 82, 54, 41.

1-Isopropyl-5-methylene-3-phenylimidazolidine-2,4-dione 4c. White solid (79%); mp = 35–37 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 1.48 (d, 2CH_3-*i*Pr, J = 7.2 Hz), 4.40–4.47 (m, CH-*i*Pr), 4.97 (d, CH_2=C, J = 2.4 Hz), 5.54 (d, CH_2=C, J = 2.1 Hz), 7.34–7.49 (m, 5H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): 19.8 (2CH_3-*i*Pr), 45.2 (CH-*i*Pr), 95.5 (CH_2=C), 126.0–131.4 (C_{arom}), 134.3 (C_q=C), 152.6 (NCON), 161.6 (CO).

5-Methylene-3-phenyl-1-[(1S)-1-phenylethyl]imidazolidine-2,4-dione 4d. Yellow solid (85%); mp = 120 °C;$[\alpha]_D^{17}$ + 0.26 (c = 2.25, AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$): 1.73 (d, CH_3, J = 7.5 Hz), 4.52 (d, CH_2=C, J = 2.1 Hz), 5.30 (d, CH_2=C, J = 2.1 Hz), 5.60 (q, CH), 7.14–7.35 (m, 10H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): 16.6 (CH_3), 50.9 (CH), 97.7 (CH_2=C), 126.3–139.4 (C_{arom}), 153.6 (C_q=C), 161.8 (NCON), 169.3 (CO).

Synthesis of Nitrones

N,α-Diphenylnitrone 5. White solid (80%); mp = 112–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.26–8.41 (m, 10H_{arom}), 7.92 (s, CH=N); ^{13}C NMR (75.5 MHz, $CDCl_3$): 121.8–149.1 (C_{arom}), 130.7 (CH=N).

C-Phenyl-N-tert-butylnitrone 6. White crystals (74%); mp = 70–72 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 1.60 (s, 3CH_3-*t*Bu), 7.38–8.29 (m, 5H_{arom}), 7.53 (s, CH=N); ^{13}C NMR (75.5 MHz, $CDCl_3$): 28.3 (3CH_3-*t*Bu), 70.8 (C-*t*Bu), 128.4–131.0 (C_{arom}), 129.9 (CH=N).

C-(2-Methoxyphenyl)-N-isopropylnitrone 7. Yellow oil (70%); ^{1}H NMR (300 MHz, $CDCl_3$): 1.43 (d, 2CH_3-*i*Pr, J = 6.3 Hz), 3.78 (OCH_3), 4.19 (m, CH-*i*Pr), 6.79–9.30 (m, 4H_{arom}), 7.88 (s, CH=N); ^{13}C NMR (75.5 MHz, $CDCl_3$): 21.2 (2CH_3-*i*Pr), 55.8 (CH-*i*Pr), 68.4 (OCH_3), 110.0–131.2 (C_{arom}), 131.5 (CH=N), 157.1 (C_q-OCH_3).

Cycloadducts 8–19: General Procedure

A solution of nitrone **5–7** (1 mmol) and methylenehydantoins **4a–d** (1 mmol) in toluene (3 mL) was stirred at 80 °C under an argon atmosphere for 24 h. The solvent was then removed, and the residue was crystallized (ethanol).

6-Benzyl-2,3,8-triphenyl-1-oxa-2,6,8-triazaspiro[4.4]nonane-7,9-dione 8. White crystals (63%); mp = 183–185 °C (ethanol); R_f 0.41 (cyclohexane/ethyl acetate 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): 2.78 (dd, H_4, $J = 10.8$ Hz, $J = 13.5$ Hz), 3.00 (dd, $H_{4'}$, $J = 6.3$ Hz, $J = 13.5$ Hz), 4.81 (dd, H_3, $J = 6.3$ Hz, $J = 10.8$ Hz), 4.85 (d, H, (CH_2-Bn), $J = 15.9$ Hz), 5.09 (d, H, (CH_2-Bn), $J = 15.9$ Hz), 7.05–7.55 (m, $20H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 43.4 (CH_2-Bn), 45.6 (C_4), 71.9 (C_3), 91.0 (C_5), 120.4–148.2 (C_{arom}); 154.9 (C_7), 169.6 (C_9), IR (KBr)/cm: $\nu_{NO} = 756$; $\nu_{C\text{-}N} = 1419$, $\nu_{C=Carom} = 1493$, $\nu_{C=O} = 1729$, $\nu_{C\text{-}H\ arom} = 3059$. HRMS calcd. for $C_{30}H_{25}N'_3O_3$ $[M + H]^+$: 476.1974; found: 476.1976. Retention time (tR) = 6.987.

6-Benzyl-2-tert-butyl-3,8-diphenyl-1-oxa-2,6,8-triazaspiro[4.4]nonane-7,9-dione 9. White crystals (71%); mp = 175–177 °C (ethanol); R_f 0.55 (cyclohexane/ethyl acetate 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): 0.92 (s, $3CH_3$-tBu), 2.49 (dd, H_4, $J = 10.8$ Hz, $J = 13.5$ Hz), 2.72 (dd, $H_{4'}$, $J = 6.6$ Hz, $J = 13.5$ Hz), 4.44 (dd, H_3, $J = 6.6$ Hz, $J = 10.8$ Hz), 4.67 (d, H, (CH_2-Bn), $J = 15.9$ Hz), 4.91 (d, H, (CH_2-Bn), $J = 15.9$ Hz), 7.15–7.38 (m, $15H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 26.7 ($3CH_3$-tBu), 43.7 (CH_2-Bn), 48.2 (C_4), 60.1 (C-tBu), 65.6 (C_3), 91.2 (C_5), 126.2–140.2 (C_{arom}), 155.3 (C_7), 170.5 (C_9). HRMS calcd. for $C_{28}H_{29}N_3O_3$ $[M + Na]^+$: 478.2106; found: 478.2101. Retention time (tR) = 7.487.

6-Benzyl-2-isopropyl-3-(2-methoxyphenyl)-8-phenyl-1-oxa-2,6,8-triazaspiro[4.4]nonane-7,9-dione 10. White crystals (55%); mp = 91–93 °C (ethanol); R_f 0.30 (cyclohexane/ethyl acetate 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): 1.13 (dd, $2CH_3$-iPr), 2.45 (dd, H_4, $J = 10.8$ Hz, $J = 13.5$ Hz), 3.05 (dd, $H_{4'}$, $J = 6.6$ Hz, $J = 13.5$ Hz), 3.32 (m, CH-iPr), 3.72 (OCH_3), 4.49 (d, H, (CH_2-Bn), $J = 15.9$ Hz), 4.83 (d, H, (CH_2-Bn), $J = 15.9$ Hz), 4.88 (t, H_3), 6.81–7.59 (m, $14H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 14.6–17.6 ($2CH_3$-iPr), 42.7 (C_4), 43.1 (CH_2-Bn), 55.1 (CH-iPr), 55.2 (OCH_3), 60.8 (C_3), 92.3 (C_5), 110.5–137.4 (C_{arom}), 154.8 (C_7), 157.0 (C_{11}), 170.4 (C_9). HRMS calcd. for $C_{28}H_{29}N_3O_4$ $[M + H]^+$: 472.2237; found: 472.2232. Retention time (tR) = 7.098.

6-Isobutyl-2,3,8-triphenyl-1-oxa-2,6,8-triazaspiro[4.4]nonane-7,9-dione 11. White crystals (60%); mp = 148–150 °C (ethanol); R_f 0.44 (cyclohexane/ethyl acetate 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): 1.10 (dd, $2CH_3$-iBu), 2.49 (m, CH-iBu), 2.91 (dd, H_4, $J = 10.2$ Hz, $J = 13.5$ Hz), 3.20 (dd, $H_{4'}$, $J = 6.9$ Hz, $J = 13.5$ Hz), 3.41 (dd, H, (CH_2-iBu), $J = 14.1$ Hz, $J = 6.6$ Hz), 3.66 (dd, H, (CH_2-iBu), $J = 14.1$ Hz, $J = 9$ Hz), 4.94 (dd, H_3, $J = 6.9$ Hz, $J = 10.2$ Hz), 7.07–7.54 (m, $15H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.7–20.9 ($2CH_3$-iBu), 28.6 (CH-iBu), 45.8 (C_4), 48.1 (CH_2-iBu), 71.4 (C_3), 91.6 (C_5), 118.5–148.6 (C_{arom}), 155.0 (C_7), 169.9 (C_9). HRMS calcd. for $C_{27}H_{27}N_3O_3$ $[M + Na]^+$: 464.1950; found: 464.1938. Retention time (tR) = 7.570.

2-Tert-butyl-6-isobutyl-3,8-diphenyl-1-oxa-2,6,8-triazaspiro[4.4]nonane-7,9-dione 12. White crystals (58%); mp = 144–146 °C (ethanol); R_f 0.58 (cyclohexane/ethyl acetate 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): 0.95 (s, $3CH_3$-tBu),

0.99 (d, $2CH_3$-*i*Bu), 2.44 (m, CH-*i*Bu), 2.60 (dd, H_4, $J = 10.5$ Hz, $J = 13.5$ Hz), 2.85 (dd, $H_{4'}$, $J = 6.9$ Hz, $J = 13.5$ Hz), 3.20 (dd, H, (CH_2-*i*Bu), $J = 14.1$ Hz, $J = 6.6$ Hz), 3.52 (dd, H, (CH_2-*i*Bu), $J = 14.1$ Hz, $J = 9.3$ Hz), 4.49 (dd, H_3, $J = 6.9$ Hz, $J = 10.5$ Hz), 7.18–7.39 (m, $10H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.5–20.9 ($2CH_3$-*i*Bu), 26.7 ($3CH_3$-*t*Bu), 28.2 (CH-*i*Bu), 47.7 (C-*t*Bu), 47.8 (C_4), 60.0 (CH_2-*i*Bu), 65.2 (C_3), 90.4 (C_5), 126.1–140.9 (C_{arom}), 154.9 (C_7), 170.5 (C_9). HRMS calcd. for $C_{25}H_{31}N_3O_3$ $[M + H]^+$: 422.2444; found: 422.2438. Retention time (*t*R) = 7.743.

2-Isopropyl-6-isobutyl-3-(2-methoxyphenyl)-8-phenyl-1-oxa-2,6,8-triazaspiro[4.4]nonane-7,9-dione 13. White crystals (50%); mp = 135–137 °C (ethanol); R_f 0.34 (cyclohexane/ethyl acetate 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): 0.90 (dd, $2CH_3$-*i*Bu), 1.14 (dd, $2CH_3$-*i*Pr), 2.23 (m, CH-*i*Bu), 2.56 (dd, H_4, $J = 8.1$ Hz, $J = 13.8$ Hz), 3.06–3.36 (m, $H_{4'}$, CH_2-*i*Bu, CH-*i*Pr), 3.87 (OCH_3), 4.91 (t, H_3), 6.90–7.65 (m, $9H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 17.9–21.8 ($2CH_3$-*i*Pr), 20.4–20.6 ($2CH_3$-*i*Bu), 28.2 (CH-*i*Bu), 43.5 (C_4), 47.7 (CH_2-*i*Bu), 55.6 (CH-*i*Pr), 55.7 (OCH_3), 61.1 (C_3), 92.6 (C_5), 110.8–132.0 (C_{arom}), 155.0 (C_7), 157.3 (C-OCH_3), 170.8 (C_9). HRMS calcd. for $C_{25}H_{31}N_3O_4$ $[M + Na]^+$: 460.2212; found: 460.2225. Retention time (*t*R) = 6.107.

6-Isopropyl-2,3,8-triphenyl-1-oxa-2,6,8-triazaspiro[4.4]nonane-7,9-dione 14. White crystals (70%); mp = 174–176 °C (ethanol); R_f 0.34 (cyclohexane/ethyl acetate 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): 1.62 (dd, $2CH_3$-*i*Pr), 2.86 (dd, H_4, $J = 10.5$ Hz, $J = 13.5$ Hz), 3.14 (dd, $H_{4'}$, $J = 6.3$ Hz, $J = 13.5$ Hz), 4.25 (m, CH-*i*Pr), 4.91 (dd, H_3, $J = 6.3$ Hz, $J = 10.5$ Hz), 6.94–7.59 (m, $15H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 21.1 ($2CH_3$-*i*Pr), 45.8 (CH-*i*Pr), 46.0 (C_4), 71.3 (C_3), 91.4 (C_5), 120.1–137.4 (C_{arom}), 148.6 (C_7), 169.6 (C_9). HRMS calcd. for $C_{26}H_{25}N_3O_3$ $[M + H]^+$: 428.1974; found: 428.1979. Retention time (*t*R) = 6.107.

2-Tert-butyl-6-isopropyl-3,8-diphenyl-1-oxa-2,6,8-triazaspiro[4.4]nonane-7,9-dione 15. White crystals (60%); mp = 147–149 °C (ethanol); R_f 0.47 (cyclohexane/ethyl acetate 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): 1.02 (s, $3CH_3$-*t*Bu), 1.61 (dd, $2CH_3$-*i*Pr), 2.66 (dd, H_4, $J = 10.8$ Hz, $J = 13.2$ Hz), 2.96 (dd, $H_{4'}$, $J = 6.6$ Hz, $J = 13.2$ Hz), 4.30 (m, CH-*i*Pr), 4.55 (dd, H_3, $J = 6.6$ Hz, $J = 10.8$ Hz), 7.29–7.49 (m, $10H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.9–21.1 ($2CH_3$-*i*Pr), 26.4 ($3CH_3$-*t*Bu), 45.5 (CH-*i*Pr), 48.6 (C_4), 59.5 (C-*t*Bu), 65.0 (C_3), 90.1 (C_5), 125.9–140.2 (C_{arom}), 153.0 (C_7), 170.1 (C_9). HRMS calcd. for $C_{24}H_{29}N_3O_3$ $[M + H]^+$: 408.2287; found: 408.2278. Retention time (*t*R) = 7.283.

2,6-Diisopropyl-3-(2-methoxyphenyl)-8-phenyl-1-oxa-2,6,8-triazaspiro[4.4]-nonane-7,9-dione 16. White crystals (60%); mp = 129–131 °C (ethanol); R_f 0.33 (cyclohexane/ethyl acetate 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): 1.13 (dd, $2CH_3$-*i*Pr), 1.15 (dd, $2CH_3$-*i*Pr), 2.50 (dd, H_4, $J = 10.5$ Hz, $J = 13.5$ Hz), 3.11 (dd, $H_{4'}$, $J = 6.6$ Hz, $J = 13.5$ Hz), 3.15 (m, CH-*i*Pr), 3.85 (OCH_3), 3.98 (m, CH-*i*Pr), 4.89 (t, H_3), 6.88–7.61 (m, $9H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 16.9–21.5 ($2CH_3$-*i*Pr), 20.8–20.9 ($2CH_3$-*i*Pr), 44.1 (C_4), 45.4 (CH-*i*Pr), 54.9 (CH-*i*Pr), 55.4 (OCH_3), 60.5 (C_3), 91.9 (C_5), 110.5–131.4 (C_{arom}), 153.0 (C_7), 157.0 (C-OCH_3), 170.3 (C_9). HRMS calcd. for $C_{24}H_{29}N_3O_4$ $[M + H]^+$: 424.2237; found: 424.2244. Retention time (*t*R = 7.164).

2,3,8-Triphenyl-6-[(1 s)-1-phenylethyl]-1-oxa-2,6,8-triazaspiro[4.4]nonane-7,9-dione 17. White crystals (70%); mp = 168–170 °C (ethanol); $[\alpha]_D^{17} - 0.3$ (c = 0.83, AcOEt); R_f 0.47 (cyclohexane/ethyl acetate 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): 1.98 (t, CH_3), 2.70 (dd, H_4, $J = 10.8$ Hz, $J = 13.5$ Hz), 2.90 (dd, $H_{4'}$, $J = 6.3$ Hz, $J = 13.5$ Hz), 4.60 (dd, H_3, $J = 6.3$ Hz, $J = 10.8$ Hz), 5.45 (quin, CH), 7.23–7.71 (m, $20H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 26.4 (CH_3), 48.3 (C_4), 52.8 (CH), 65.2 (C_3), 90.5 (C_5), 125.8–141.9 (C_{arom}), 153.3 (C_7), 169.8 (C_9). HRMS calcd. for $C_{31}H_{27}N_3O_3$ $[M + H]^+$: 490.2131; found: 490.2138. Retention times $tR_1 = 7.790$, $tR_2 = 8.970$.

2-Tert-butyl-3,8-diphenyl-6-[(1 s)-1-phenylethyl]-1-oxa-2,6,8-triazaspiro[4.4]nonane-7,9-dione 18. White crystals (52%); mp = 178–180 °C (ethanol); $[\alpha]_D^{17} - 0.17$ (c = 1.68, AcOEt); R_f 0.44 (cyclohexane/ethyl acetate 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): 0.96 (s, $3CH_3$-*t*Bu), 1.92 (d, CH_3), 2.64 (dd, H_4, $J = 10.8$ Hz, $J = 13.5$ Hz), 2.81 (dd, $H_{4'}$, $J = 6.3$ Hz, $J = 13.5$ Hz), 4.50 (dd, H_3, $J = 6.3$ Hz, $J = 10.8$ Hz), 5.25 (quin, CH), 7.18–8.23 (m, $15H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 26.8 (CH_3), 28.7 ($3CH_3$-*t*Bu), 48.7 (C_4), 53.1 (CH), 60.1 (C_3), 65.6 (C-*t*Bu), 90.9 (C_5), 126.1–142.2 (C_{arom}), 153.8 (C_7), 170.1 (C_9). HRMS calcd. for $C_{29}H_{31}N_3O_3$ $[M + H]^+$: 470.2444; found: 470.2450. Retention times $tR_1 = 7.720$, $tR_2 = 8.977$.

2-Isopropyl-3-(2-methoxyphenyl)-8-phenyl-6-[(1 s)-1-phenylethyl]-1-oxa-2,6,8-triazaspiro[4.4]nonane-7,9-dione 19. Yellow solid (74%); mp = 140 °C (ethanol); $[\alpha]_D^{17} - 0.15$ (c = 0.83, AcOEt); R_f 0.36 (cyclohexane/ethyl acetate 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): 1.41 (d, $2CH_3$-*i*Pr), 1.80 (d, CH_3-CH, $J = 6.6$ Hz), 2.45 (dd, H_4, $J = 8.1$ Hz, $J = 13.5$ Hz), 3.05 (dd, $H_{4'}$, $J = 8.1$ Hz, $J = 13.5$ Hz), 3.20 (m, CH-*i*Pr), 3.77 (OCH_3), 4.15 (q, CH-CH_3), 4.88 (t, H_3), 6.78–7.41 (m, $14H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 21.6 ($2CH_3$-*i*Pr), 42.5 (C_4), 55.9 (CH-*i*Pr), 56.0 (OCH_3), 68.5 (C_3), 93.5 (C_5), 110.1–131.7 (C_{arom}), 158.8 (C_7), 170.1 (C-OCH_3), 171.2 (C_9). HRMS calcd. for $C_{29}H_{31}N_3O_4$ $[M + Na]^+$: 508.2212; found: 508.2224. Retention times $tR_1 = 7.591$, $tR_2 = 8.807$.

Reduction of Compound 8

To a suspension of 0.4 mmol of pure spirohydantoin **8** in 9 mL of acetic acid/water (1:2), 1.6 mmol of zinc were added. The reaction mixture was heated at 70 °C for 48 h. The solution was cooled to room temperature. Zinc salts were filtered off, and the filtrate was concentrated. The residue was partitioned between 10% ammonium hydroxide/methylene chloride. The aqueous layer was extracted with CH_2Cl_2, and the combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography [SiO_2–cyclohexane/ethyl acetate (80:20)] to give the compounds **20**.

(2-Anilino-2-phenylethyl)-1-benzyl-5-hydroxy-3-phenylimidazolidine-2,4-dione 20. Yellow solid (49%); mp = 164–166 °C; R_f 0.38 (cyclohexane/ethyl acetate 90:10); ^{1}H NMR (300 MHz, DMSO-d_6): 2.12 (d, H_4, $J = 15$ Hz), 2.50 (t, $H_{4'}$, $J = 13.5$ Hz), 3.84 (dd, H_3, $J = 13.5$ Hz, $J = 2.7$ Hz), 3.96 (d, H_{10}, $J = 16.5$ Hz), 4.75 (2 s, NH and OH), 5.17 (d, $H_{10'}$, $J = 16.5$ Hz), 6.64–7.40 (m, $20H_{arom}$); ^{13}C NMR (75.5 MHz, DMSO-d_6): 43.2 (C_4), 45.6 (C_{10}), 52.8 (C_3), 66.0 (C_5),

116.9–143.6 (C_{arom}), 156.2 (C_7), 174.3 (C_9); IR (KBr)/cm^{-1}: $\nu_{C\text{-}N} = 1410$, $\nu_{C=Carom} = 1494$, $\nu_{C=O} = 1721$, $\nu_{C\text{-}Harom} = 2924$; $\nu_{N\text{-}H\&O\text{-}H} = 3437$. HRMS calcd. for $C_{30}H_{27}N_3O_3$ $[M + H]^+$: 478.2131; found: 478.2129.

ACKNOWLEDGMENT

The authors are grateful to DGRSRT (Direction Générale de la Recherche Scientifique et de la Rénovation Technologique) of the Tunisian Ministry of Higher Education, Scientific Research, and Technology for the financial support.

REFERENCES

1. Huisgen, R. 1,3-Dipolar cycloadditions: Past and future. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565–598.
2. Blanarikova-Hlobilova, I.; Fisera, L.; Pronayova, N.; Koman, M. 1,3-Dipolar cycloadditions of D-erythrose- and D-threose-derived alkenes with nitrones. *Collect. Czech. Chem. Commun.* **2003**, *68*, 951–964.
3. Herrera, R.; Nagarajan, A.; Morales, M. A.; Mendez, F.; Jimenez-Vazquez, H. A.; Zepeda, L. G.; Tamariz, J. Regio- and stereoselectivity of captodative olefins in 1,3-dipolar cycloadditions: A DFT/HSAB theory rationale for the observed regiochemistry of nitrones. *J. Org. Chem.* **2001**, *66*, 1252–1263.
4. Ishar, M. P. S.; Singh, G.; Kumar, K.; Singh, R. Investigations on peri-, regio- and stereoselectivities in thermal cycloadditions involving *C*-(4-oxo-4*H*[1]benzopyran-3-yl)-*N*-phenylnitrones: Role of steric factors and secondary interactions in 1,3-dipolar cycloadditions. *Tetrahedron* **2000**, *56*, 7817–7828.
5. Shih, H.-W.; Cheng, W.-C. Solution-phase parallel synthesis of highly diverse spiroisoxazolinohydantoins. *Tetrahedron Lett.* **2008**, *49*, 1008.
6. DeShong, P.; Leginus, J. M.; Lander, S. W. A stereoselective approach to the synthesis of allylic and homoallylic amines. *J. Org. Chem.* **1986**, *51*, 574–576.
7. Kametani, T.; Chu, S.-D.; Honda, T. Chiral synthesis of 3-[(R)-1-hydroxyethyl]-4-oxoazetidin-2-yl acetate using an asymmetric 1,3-dipolar cycloaddition reaction. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1593–1597.
8. Dondoni, A.; Marra, A. Methods for anomeric carbon-linked and fused sugar amino acid synthesis: The gateway to artificial glycopeptides. *Chem. Rev.* **2000**, *100*, 4395–4421.
9. (a) Asrof, A. S. K.; Khan, J. H.; Wazeer, M. I. M. The regiochemistry and stereochemistry of 1,3-dipolar cycloaddition of cyclic nitrones. *Tetrahedron* **1988**, *44*, 5911–5920; (b) Hall, A.; Meldrum, K. P.; Therond, P. R.; Wightman, R. H. Synthesis of hydroxylated pyrrolizidines related to alexine using cycloaddition reactions of functionalized cyclic nitrones. *Synlett* **1997**, 123–125; (c) Goti, A.; Fedi, V.; Nannelli, L.; De Sarlo, F.; Brandi, A. Cycloaddition of an enantiopure cyclic nitrone to maleate: Straightforward synthesis of the necine base (–)-hastanecine. *Synlett* **1997**, 577–579.
10. Ware, E. The chemistry of the hydantoins. *Chem. Rev.* **1950**, *46*, 403.
11. Brandstetter, T. W.; de la Fuente, C.; Kim, Y.-H.; Johnson, L. N.; Crook, S.; Lilley, P. M. Q.; Watkin, D. J.; Tsitsanou, K. E.; Zographos, S. E.; Chrysina, E. D.; Oikonomakos, N. G.; Fleet, G. W. J. Glucofuranose analogues of hydantocidin. *Tetrahedron* **1996**, *52*, 10721.
12. Bleicher, K. H.; Thrich, Y. W.; De Boni, M.; Kolczewski, S.; Hoffmann, T.; Sleight, A. J. Parallel solution- and solid-phase synthesis of spirohydantoin derivatives as neurokinin-1 receptor ligands. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2519.

13. Struck, R. F.; Kirk, M. C.; Rice, L. S.; Suling, W. J. Isolation, synthesis, and antitumor evaluation of spirohydantoin aziridine, a mutagenic metabolite of spirohydantoin mustard. *J. Med. Chem.* **1986**, *29*, 1319.
14. Matsukura, M.; Daiku, Y.; Ueda, K.; Tanaka, S.; Igarashi, T.; Minami, N. Synthesis and antiarrhythmic activity of 2,2-dialkyl-1′-(N-substituted aminoalkyl)-spiro-[chroman-4, 4′-imidazolidine]-2′,5′-diones. *Chem. Pharm. Bull.* **1992**, *40*, 1823.
15. Novelli, A. *Anales Farm. y Bioquim.* **1954**, *21*, 81; *Chem. Abstr.* **1956**, *50*, 4922d.
16. Baker, J. T.; Wells, R. J. *Natural Products as Medicinal Reagents*; J. L. Beal, E. Reinhard (Eds.); Hippokrates Verlag: Stuttgart, 1981; p. 299.
17. (a) Mio, S.; Ichinose, R.; Goto, K.; Sugai, S.; Sato, S. Synthetic studies on (+)-hydantocidin (1): A total synthesis of (+)-hydantocidin, a new herbicidal metabolite from microorganism. *Tetrahedron* **1991**, *47*, 2111; (b) Sano, H.; Sugai, S. Stereoselective synthesis of (+)-hydantocidin. *Tetrahedron* **1995**, *51*, 4635; (c) Harrington, P. M.; Jung, M. E. Stereoselective bromination of b-ribofuranosyl amide: Enantioselective synthesis of (+)-hydantocidin. *Tetrahedron Lett.* **1994**, *35*, 5145.
18. Gomez-Monterrey, I.; Santelli, G.; Campiglia, P.; Califano, D.; Falasconi, F.; Pisano, C.; Vesci, L.; Lama, T.; Grieco, P.; Novellino, E. Synthesis and cytotoxic evaluation of novel spirohydantoin derivatives of the dihydrothieno[2,3-*b*]naphtho-4,9-dione system. *J. Med. Chem.* **2005**, *48*, 1152–1157.
19. (a) Bichard, C. J. F.; Mitchell, E. P.; Wormald, M. R.; Watson, K. A.; Johnson, L. N.; Zographos, S. E.; Koutra, D. D.; Oikonomakos, N. G.; Fleet, G. W. J. Potent inhibition of glycogen phosphorylase by a spirohydantoin of glucopyranose: First pyranose analogues of hydantocidin. *Tetrahedron Lett.* **1995**, *36*, 2145; (b) Brandstetter, T. W.; Kim, Y.-H.; Chan Son, J.; Taylor, H. M.; Lilley, P. M. Q.; Watkin, D. J.; Johnson, L. N.; Oikonomakos, N. G.; Fleet, G. W. Spirohydantoins of glucofuranose: Analogues of hydantocidin. *Tetrahedron Lett.* **1995**, *36*, 2149.
20. (a) Yamagishi, M.; Yamada, Y.; Ozaki, K.-I.; Da-te, T.; Okamura, K.; Suzuki, M.; Matsumoto, K. Preparation of optically pure 3′-methylspiro[imidazolidine-4,4′(1′H)-quinazoline]-2,2′,5(3′H)-trione by combination of optical resolution and racemization. *J. Org. Chem.* **1992**, *57*, 1568; (b) Unno, R.; Yamaguchi, T.; Usui, T.; Kakigami, T.; Fukushima, M.; Kuhinaru, M.; Yutaka, B.; Masayasu, K. Synthesis and aldose reductase inhibitory activity of 2-substituted 6-fluoro-2,3-dihydrospiro[4H-1-benzopyran-4,4′-imidazolidine2′,5′-diones. *Chem. Pharm. Bull.* **1994**, *42*, 1474.
21. Porzi, G.; Sandri, S. Enantioselective synthesis of (R)- and (S)-α-amino acids using (6S)- and (6R)-6-methyl-morpholine-2,5-dione derivatives. *Tetrahedron: Asymmetry* **1996**, *7*, 189–196.
22. Leon-Romo, J. L.; Virues, C. I.; Avina, J.; Regla, I.; Juaristi, E. Preparation of (R)- and (S)-α-methyldopa from a chiral hydantoin containing the α-phenylethyl group. *Chirality* **2002**, *14*, 144–150.
23. (a) Ksandes, G. M.; McMurry, J. E.; Johnson, M. A method for the synthesis of unsaturated carbonyl compounds. *J. Org. Chem.* **1977**, *42*, 1180–1185; (b) Ueda, M.; Takahashi, M.; Suzuki, T.; Imai, Y., Pittman Jr., C. U. Polymerization of α-methylene-*N*-methylpyrrolidone. *J. Polym. Sci., Polym. Phys. Ed.* **1983**, *21*, 1139–1149.
24. Huisgen, R.; Hauck, H.; Grashey, R.; Seidl, H. 1.3-Dipolare cycloadditionen, XLIII: Isoxazolidine aus Nitronen mit α,β-ungesättigten Carbonestern oder Nitrilen. *Chem. Ber.* **1968**, *101*, 2568.
25. Harikawa, H.; Nishitani, T.; Iwasaki, T.; Inoue, I. A short, efficient, synthetic pathway to the 6,7,8,9-tetrahydro-5H-dibenz[d,f]azonine system. *Tetrahedron Lett.* **1979**, *20*, 2193.
26. (a) Rigolet, S.; Mélot, J. M.; Vebrel, J.; Chiaroni, A.; Riche, C. The reaction of α- and ω-methylenelactams with nitrons: Influence of electronic and geometric factors on the stereoselectivity of their 1,3-dipolar cycloaddition. *J. Chem. Soc., Perkin Trans. 1* **2000**,

1095; (b) Roussel, C.; Fihi, R.; Ciamala, K.; Vébrel, J.; Zair, T.; Riche, C. Spiroheterocycles from reaction of nitrones with methylene-γ-butyrolactones and some of their rearrangements. *Org. Biomol. Chem.* **2003**, *1*, 2689–2698.
27. Cacciarini, M.; Cordero, F. M.; Faggi, C.; Goti, A. Cycloaddition reactions of *C,N*-diphenylnitrone to methylene-γ-butyrolactones. *Molecules* **2000**, *5*, 637.
28. (a) Tufariello, J. J. 1,3-Dipolar cycloaddition chemistry. In *Cycloaddition Chemistry*; A. Padwa (Ed.); Wiley: New York, 1984; vol. 2, p. 83; (b) Confalone, P. N.; Huie, E. M. The [3 + 2] nitrone–olefin cycloaddition reaction. *Org. React.* **1988**, *36*, 1–173 ; (c) Torsell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: Weinheim, 1988; pp. 33–37.
29. Chiacchio, U.; Corsaro, A.; Pistara, V.; Rescifina, A.; Romeo, G.; Romeo, R. An asymmetric approach to pyrrolidinone and pyrrolizidinone systems by intramolecular oxime–olefin cycloaddition. *Tetrahedron* **1996**, *52*, 7875.
30. Kamm, O. β-Phenylhydroxylamine. *Organic Syntheses Coll.* **1941**, *1*, 445.
31. Brüning, I.; Gashey, R.; Hauck, M.; Huisgen, R.; Seidl, M. 2,3,5-Triphenylisoxazolidine. *Org. Synth. Coll.* **1966**, *5*, 1124.
32. Barton, D.; Ollis, W. D. *Comprehensive Organic Chemistry*; I. O. Sutherland: Oxford, 1979; vol. 2, p. 1081.
33. Kraiem, J.; Kacem, Y.; Khiari, J.; Ben Hassine, B. Stereospecific synthesis of 2-alkyl-3-aryloxaziridines from prochiral and chiral N-arylidenealkylamines by use of the benzonitrile–hydrogen peroxide system. *Synth. Commun.* **2001**, *31*, 263.