HETEROCYCLES, Vol. 81, No. 3, 2010, pp. 707 - 715. © The Japan Institute of Heterocyclic Chemistry
Received, 20th November, 2009, Accepted, 24th December, 2009, Published online, 28th December, 2009
DOI: 10.3987/COM-09-11874

REGIOSELECTIVE SYNTHESIS AND STRUCTURE OF NEW SPIRO-ISOQUINOLINEDIONE DERIVATIVES

Nafâa Jegham, Yakdhane Kacem, and Béchir Ben Hassine*

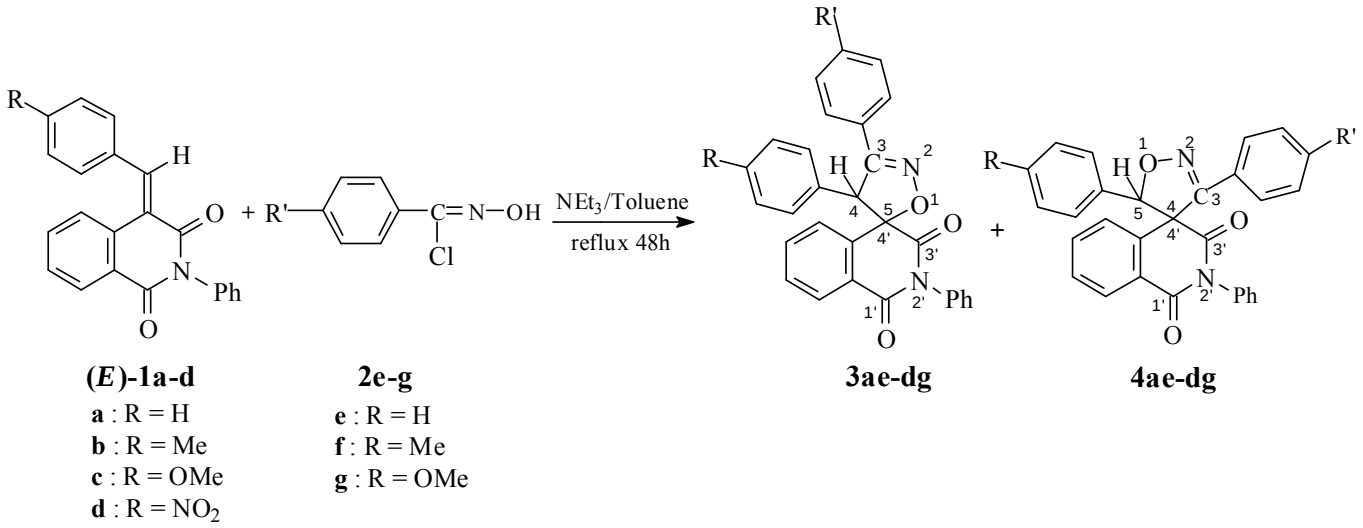
Laboratoire de Synthèse Organique Asymétrique et Catalyse Homogène (01 UR 1201), Faculté des Sciences de Monastir, Avenue de l'Environnement, 5019, Monastir, Tunisie

Abstract – New spiro-isoquinolinoisoxazolines were prepared by regioselective 1,3-dipolar cycloaddition of 4-arylidene-isoquinoline-1,3-dione derivatives **1a-d** with arylnitrile oxides **2e-g**. In all cases, two regioisomers **3ae-dg** and **4ae-dg** were isolated with comparable ratios. Regioselectivity was established by unambiguous structural NMR assignments and X-ray diffraction analysis.

4-Spiroisoquinoline derivatives have gained an increasing interest in recent years thanks to their potential bioactivity[1,2] and their versatile utility as precursors in the preparation of numerous biologically-active products.[3] These compounds have been synthesised using various methods[4] essentially by 1,3-dipolar cycloaddition reactions to the exocyclic C-C double bond of specific isoquinoline-4-ylidene derivatives. This method has proven to be an excellent synthetic route however, few examples of the synthesis of such systems by means of cycloaddition are reported in the literature.[5] 4-Spiroisoquinoline can also be prepared by an intramolecular cyclisation with suitable chain at position 4 of isoquinoline derivatives.[6]
As an extension of our work in the field towards the synthesis of spiroisoquinolines,[7] we report herein an efficient and practical procedure for the preparation of new spiro-isoquinolinoisoxazolines **3ae-dg** and **4ae-dg** by 1,3-dipolar cycloaddition of ylidene isoquinoline-1,3-dione derivatives with arylnitrile oxides. This approach also allows access to spiroheterocycles having very important biological activities.[8]

The synthetic route to the targeted spiro-isoquinolinoisoxazolines **3ae-dg** and **4ae-dg** is outlined in Scheme 1. Dipolarophiles **1a-d** were obtained by the condensation of aromatic aldehydes with *N*-phenyl-(2*H*)-homophthalimide. Arylnitrile oxides **2e-g** were easily generated *in situ* from benzohydroxyaminoyl chlorides with triethylamine in toluene following a known procedure.[9] Cycloaddition reaction of dipolarophiles **1a-d** with the arylnitrile oxides **2e-g** at reflux of toluene within

48 h afforded the two regioisomers spiro-isoquinolinoisoxazolines **3ae-dg** and **4ae-dg** with good chemical yields and comparable ratios as shown in Table1.



Scheme 1. [3+2] Cycloaddition reaction of benzohydroxyaminoyl chlorides **2e-g** with (*E*)-4-arylidene-isoquinoline-1,3-diones **1a-d**

Table 1. Selected data for compounds **3ae-dg** and **4ae-dg**

Entry	R	R'	Cycloadducts 3/4	Ratios 3/4	^{1}H NMR (δH_4 and δH_5)	^{13}C NMR ($\delta C_{5,4'}$ and $\delta C_{4,4'}$)
1	H	H	**3ae/4ae**	68/32	5.24/6.26	90.74/70.82
2	Me	H	**3be/4be**	65/35	5.23/6.25	90.80/70.77
3	OMe	H	**3ce/4ce**	71//29	5.21/6.23	90.39/70.83
4	NO_2	H	**3de/4de**	73/27	5.25/6.28	90.90 /70.87
5	H	Me	**3af/4af**	67/33	5.22/6.19	90.61/70.90
6	Me	Me	**3bf/4bf**	66/34	5.21/6.16	90.67/70.86
7	OMe	Me	**3cf/3'cf**	70/30	5.20/6.12	90.58/70.85
8	NO_2	Me	**3df/4df**	71/29	5.24/6.22	90.76/70.94
9	H	OMe	**3ag/4ag**	72/28	5.21/6.29	90.57/70.94
10	Me	OMe	**3bg/4bg**	70/30	5.20/6.25	90.57/70.92
11	OMe	OMe	**3cg/4cg**	69/31	5.18/6.21	90.53/70.92
12	NO_2	OMe	**3dg/4dg**	68/32	5.20/6.27	90.60/70.97

During this study, we have submitted dipolarophiles **1a-d** to cycloaddition reaction with the arylnitrile oxides **2e-g** leading to a mixture of two adducts as evidenced by TLC and ^{1}H NMR examination of the crude mixture. The pairs of cycloadducts **3ae-dg** and **4ae-dg** are usually formed in fair yields and have been separated by column chromatography. The structures of two cycloadducts were established on the basis of spectroscopic and crystallographic data. According to X-ray crystal analysis the two cycloadducts are regioisomers as result of two different ways of approach of benzohydroxyaminoyl chlorides (**2e-g**) to

the C=C exocyclic double bond of (*E*)-4-arylidene-*N*-phenyl-(2*H*)-isoquinoline-1,3-dione (**1a-d**). In each case, the mixture of two regioisomers is obtained in comparable ratios ranging closely around 70/30. These ratios were determined by the integration of the benzylic protons H-4 and H-5 signals in the NMR spectra of the crude mixture and closely correspond to those obtained in the separation. In order to have more regioselectivity, the cycloadditions have been performed in different solvents: toluene, benzene and chloroform at reflux and at room temperature. Unfortunately, we have found that variation of reaction conditions showed very little modifications in the ratios of formed regioisomers.

The regiochemistry of the reaction was not similar to that observed in the case of an olefin activated by an electron-withdrawing group, which was always situated at the position 5 of the resulting spiroisoxazoline derivatives.[7,10] The ^{1}H NMR spectra of regioisomers **3ae-dg** exhibited a signal around δ= 5.18-5.25 ppm attributed to the proton H-4. The ^{13}C NMR data also confirmed this result. The chemical shifts of the spiro carbon atoms (C-5, 4') were found to be between 90.39-90.90 ppm because of the deshielding effect of the oxygen atom. In the case of structures **4ae-dg**, the ^{1}H NMR spectra are similar to that of regioisomers **3ae-dg** but show more deshielded signals for H-5 (δ=6.12-6.29 ppm) while chemical shift values of the spiro carbon atoms (C-4,4') were between 70.77-70.97 ppm. The suggested regiochemistry of **3ae-dg** and **4ae-dg** was furthermore supported by X-ray analysis (**Figures 1** and **2**). The cycloadducts **3ae-dg** and **4ae-dg** present respectively two new chiral centers, i.e the quaternary spiroatom and C-4 or C-5 of isoxazole ring. The relative stereochemistry of these carbon results from preservation of the (*E*) configuration of the initial olefin. The stereochemistry of the cycloadducts was corroborated by an X-ray crystal analysis of the spiroadducts **3cg** and **4ag**.

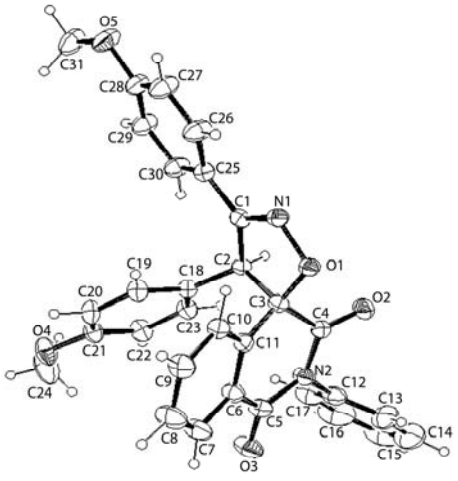


Figure 1. ORTEP of compound **3cg**

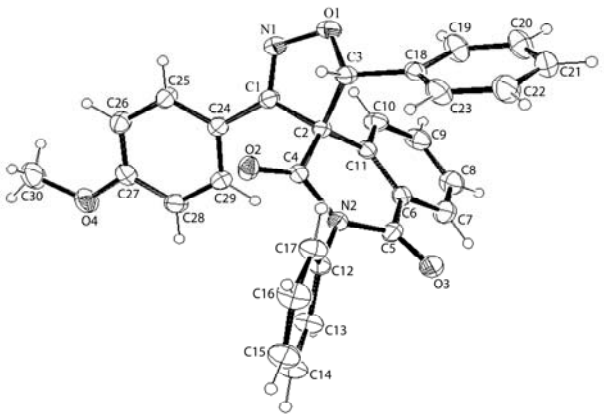


Figure 2. ORTEP of compound **4ag**

We have shown an efficient and simple route to 4-spiroisoquinoline derivatives by 1,3-dipolar cycloaddition which continue to attract the attention of both synthetic chemists and pharmacologists. The

cycloaddition reaction of arylnitrile oxides with (*E*)-4-arylideneisoquinoline-1,3-dione derivatives leads to two regioisomers and the regiochemistry of the reaction was explained using spectroscopic and crystallographic data.

EXPERIMENTAL

Reactions were carried out under an atmosphere of dry N_2. Solvents were purified by standard methods and freshly distilled under nitrogen and dried before use. *N*-Phenyl homophthalimide were prepared according to the reported method.[11] Melting points were determined on a Kofler bank and were uncorrected. NMR spectra were recorded on a Bruker-spectrospin AC 300 spectrometer, operating at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C. Chemical shifts were measured relative to TMS in $CDCl_3$ as solvent. Elemental analyses were carried out by the service of Microanalyse of the ''Institut National de Recherche et d'Analyse Physico-Chimique de Tunis''.

The crystal data for $C_{31}H_{24}N_2O_5$ (**3cg**) and $C_{30}H_{22}N_2O_4$ (**4ag**) were recorded on a Bruker-APEX II CCD diffractometer. **3cg**: M = 504.52, Monoclinic, $P2_1/c$, a = 12.2441 (6) Å, b = 9.73941 (4) Å, c =23.0227 (11) Å, V = 2610.1 (2) Å^3, Z = 4, D_c = 1.284 Mg/m^3, X-ray source Mo Kα (radiation), k = 0.71070 Å, F (000) = 1056, T = 296(2) K, white prism 0.44 × 0.30 × 0.23 mm. The structure was worked out by direct methods and refined anisotropically using a full-matrix with least squares based on F^2 to give R1 = 0.0498, wR2 = 0.1018 for 5398 independent observed reflections and 416 parameters. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center as a supplementary publication number CCDC 738431. **4ag**: M= 474.50, Monoclinic, $P2_1/c$, a = 9.8754 (3) Å, b =22.7765 (8) Å, c =10.7281 (4) Å, V =2359.85 (14) Å^3, Z =4, D_c = 1.336 Mg/m^3, X-ray source Mo Kα (radiation), k = 0.71070 Å, F (000) = 992, T = 293(2) K, white prism 0.30 × 0.20 × 0.18 mm. The structure was worked out by direct methods and refined anisotropically using a full-matrix with least squares based on F^2 to give R1 = 0.0550, wR2 = 0.1588 for 5602 independent observed reflections and 326 parameters. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center as a supplementary publication number CCDC 735594. Copies of the Crystallographic 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).

General procedure for the preparation of the dipolarophiles

(*E*)-4-Arylidene-*N*-phenyl-(2*H*)-isoquinoline-1,3-dione were obtained by the condensation of aromatic aldehydes with *N*-phenyl-(2*H*)-homophthalimide in dry chloroform in the presence of piperidine. The residue was recrystallised from EtOH to give products (**1a-d**).

General procedure for the preparation of the spirocycloadducts

A magnetically stirred solution of (*E*)-4-arylidene-*N*-phenyl-(2*H*)-isoquinoline-1,3-dione (**1a-d**) and the appropriate precursor of benzohydroxyaminoyl chlorides (**2e-g)** in dry toluene, was refluxed under nitrogen for 15 min. Et_3N (2 mL) was then added and the mixture was stirred and refluxed for 48 h. After the filtration of triethylamine hydrochloride, the solvent was evaporated and the residue was purified by chromatography on silica gel (eluent: cyclohexane-AcOEt, 90:10).

(4*S,5:4'*R**)-Spiro[3,4-diphenylisoxazoline-5,4'-(2'-phenyl)isoquinoline-1',3'-dione**] **(3ae):** Yield (60%); white solid; Mp 196 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.24 (s, 4-H), 6.67-7.79 (m, aromatic H) ppm; ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ 67.00 (C-4), 90.74 (C-5.4'), 125.17-159.09 (C-3 and aromatic C), 168.40 (C=O); 171.92 (C=O) ppm. Anal. Calcd for $C_{29}H_{20}N_2O_3$: C, 78.36; H, 4.54; N, 6.30. Found: C, 78.44; H, 4.62; N, 6.40.

(5*R,4:4'*R**)-Spiro[3,5-diphenylisoxazoline-4,4'-(2'–phenyl)isoquinoline-1',3'-dione] (4ae):** Yield (22%); yellow solid; Mp 176 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.26 (s,5-H) , 6.75-8.03 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 97.52 (C-5), 70.82 (C-4,4'), 124.94-159.84 (C-3 and aromatic C), 168.35 (C=O), 171.22 (C=O) ppm.

(4*S,5:4'*R**)-Spiro[3-phenyl-4-(*p*-tolyl)isoxazoline-5,4'-(2'-phenyl)isoquinoline-1',3'-dione] (3be):** Yield (59%); white solid; Mp 230 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, CH_3), 5.23 (s, 4-H), 6.57-8.16 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.62 (CH_3), 66.82 (C-4), 90.80 (C-5,4'), 124.83-159.73 (C-3 and aromatic C), 168.58 (C=O), 172.06 (C=O) ppm.

(5*R,4:4'*R**)-Spiro[3-phenyl-5-(*p*-tolyl)isoxazoline-4,4'-(2'-phenyl)isoquinoline-1',3'-dione] (4be):** Yield (26%); orange solid; Mp 188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, CH_3), 6.25 (s, 5-H), 6.78-8.00 (m, aromatic H) ppm; ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ 21.47 (CH_3), 97.08 (C-5),70.77 (C-4,4'), 124.19-160.15 (C-3 and aromatic C), 167.75 (C=O), 171.50 (C=O) ppm. Anal. Calcd for $C_{30}H_{22}N_2O_3$: C, 78.59; H, 4.84; N, 6.11. Found: C, 78.55; H, 4.76; N, 6.19.

(4*S,5:4'*R**)-Spiro[4-(*p*-anisyl)-3-phenylisoxazoline-5,4'-(2'-phenyl)isoquinoline-1',3'-dione] (3ce):** Yield (58%); white solid; Mp 170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, OCH_3), 5.21 (s, 4-H), 6.57-8.26 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.24 (OCH_3), 66.20 (C-4), 90.39 (C-5,4'), 114.77-161.23 (C-3 and aromatic C), 168.31 (C=O), 171.67 (C=O) ppm; Anal. Calcd for $C_{30}H_{22}N_2O_4$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.99; H, 4.77; N, 5.98.

(5*R,4:4'*R**)-Spiro[5-(*p*-anisyl)-3-phenylisoxazoline-4,4'-(2'-phenyl)isoquinoline-1',3'-dione] (4ce):** Yield (21%); orange solid; Mp 207 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, OCH_3), 6.23 (s, 5-H), 6.64-8.32(m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.48 (OCH_3), 97.00 (C-5), 70.83 (C-4,4'), 115.64-161.78 (C-3 and aromatic C), 166.93 (C=O), 171.52 (C=O) ppm.

(4*S,5:4'*R**)-Spiro[4-(*p*-nitrophenyl)-3-phenylisoxazoline-5,4'-(2'-phenyl)isoquinoline-1',3'-dione]**

(3de): Yield (65%); orange solid; Mp 212 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (s, 4-H), 7.05-8.26 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 67.20 (C-4), 90.90 (C-5,4'), 125.50-159.93 (C-3 and aromatic C), 168.46 (C=O), 172.20 (C=O) ppm.

(5*R,4:4'*R**)-Spiro[5-(*p*-nitrophenyl)-3-phenylisoxazoline-4,4'-(2'-phenyl)isoquinoline-1',3'-dione] (4de):** Yield (20%); yellow solid; Mp 165 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (s, 5-H), 7.10-8.20 (m, aromatic H) ppm; ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ 97.60 (C-5), 70.87 (C-4,4'), 124.64-160.34 (C-3 and aromatic C), 168.43 (C=O), 171.40 (C=O) ppm; Anal. Calcd for $C_{29}H_{19}N_3O_5$: C, 71.16; H, 3.91; N, 8.58. Found: C, 71.09; H, 3.80; N, 8.65.

(4*S,5:4'*R**)-Spiro[4-phenyl-3-(*p*-tolyl)isoxazoline-5,4'-(2'–phenyl)isoquinoline-1',3'-dione] (3af):** Yield (61%); white solid; Mp 190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, CH_3), 5.22 (s, 4-H), 6.75-8.00 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.88 (CH_3), 67.11 (C-4), 90.61 (C-5,4'), 125.19-159.25 (C-3 and aromatic C), 164.28 (C=O), 172.03 (C=O) ppm.

(5*R,4:4'*R**)-Spiro[5-phenyl-3-(*p*-tolyl)isoxazoline-4,4'-(2'-phenyl)isoquinoline-1',3'-dione] (4af):** Yield (23%); yellow solid; Mp 210 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, CH_3), 6.19 (s, 5-H), 6.56-7.96 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.90 (CH_3), 96.75 (C-5), 70.90 (C-4,4'), 124.43-159.41 (C-3 and aromatic C), 163.63 (C=O), 171.52 (C=O) ppm.

(4*S,5:4'*R**)-Spiro[3-(*p*-tolyl)-4-(*p*-tolyl)isoxazoline-5,4'-(2'-phenyl)isoquinoline-1',3'-dione] (3bf):** Yield (60%); colourless solid; Mp 240 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, CH_3), 2.32 (s, CH_3), 5.21(s, 4-H), 6.75-8.01 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.43 (CH_3), 21.65 (CH_3), 67.00 (C-4), 90.67 (C-5,4'), 124.92-160.30 (C-3 and aromatic C), 164.26 (C=O), 172.09 (C=O) ppm. Anal. Calcd for $C_{31}H_{24}N_2O_3$: C, 78.80; H, 5.12; N, 5.93. Found: C, 78.71; H, 5.23; N, 5.99.

(5*R,4:4'*R**)-Spiro[3-(*p*-tolyl)-5-(*p*-tolyl)isoxazoline-4,4'-(2'-phenyl)isoquinoline-1',3'-dione] (4bf):** Yield (25%); yellow solid; Mp 215 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, CH_3), 2.34 (s, CH_3), 6.16 (s, 5-H), 6.85-8.09 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.51 (CH_3), 21.77 (CH_3), 96.94 (C-5), 70.86 (C-4,4'), 124.13-160.09 (C-3 and aromatic C), 163.68 (C=O), 171.54 (C=O) ppm.

(4*S,5:4'*R**)-Spiro[4-(*p*-anisyl)-3-(*p*-tolyl)isoxazoline-5,4'-(2'-phenyl)isoquinoline-1',3'-dione] (3cf):** Yield (62%); colourless solid; Mp 230 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, CH_3), 3.65 (s, OCH_3), 5.20 (s, 4-H), 6.80-8.23 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.65 (CH_3) 55.57 (OCH_3) 66.66 (C-4), 90.58 (C-5,4'), 115.07-161.41 (C-3 and aromatic C), 164.33 (C-1), 172.13 (C-2) ppm. Anal. Calcd for $C_{31}H_{24}N_2O_4$: C, 76.21; H, 4.95; N, 5.73. Found: C, 76.15 ; H, 4.86; N, 5.82.

(5*R,4:4'*R**)-Spiro[5-(*p*-anisyl)-3-(*p*-tolyl)isoxazoline-4,4'-(2'-phenyl)isoquinoline-1',3'-dione] (4cf):** Yield (21%); orange solid; Mp 195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, CH_3), 3.78 (s, OCH_3), 6.12 (s, 5-H), 6.55-8.02 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.78 (CH_3), 55.82 (OCH_3), 96.87 (C-5),70.85 (C-4,4'), 114.33-161.58 (C-3 and aromatic C), 163.66 (C=O), 171.57 (C=O) ppm.

(4*S,5:4'*R**)-Spiro[4-(*p*-nitrophenyl)-3-(*p*-tolyl)isoxazoline-5,4'-(2'-phenyl)isoquinoline-1',3'-dione] (3df):** Yield (63%); colourless solid; Mp 220 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, CH_3), 5.24 (s, 4-H), 6.80-8.10 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.76 (CH_3), 67.24 (C-4), 90.76 (C-5,4'), 125.64-160.41 (C-3 and aromatic C), 164.20 (C=O), 172.06 (C=O) ppm. Anal. Calcd for $C_{30}H_{21}N_3O_5$: C, 71.56; H, 4.20; N, 8.35. Found: C, 71.50; H, 4.12; N, 8.23.

(5*R,4:4'*R**)-Spiro[(5-(*p*-nitrophenyl)-3-(*p*-tolyl)isoxazoline-4,4'-(2'-phenyl)isoquinoline-1',3'-dione] (4df):** Yield (20%); orange solid; Mp 190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, CH_3), 6.22 (s, 5-H), 7.01-8.08 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.80 (CH_3), 96.89 (C-5), 70.94 (C-4,4'), 125.33-160.22 (C-3 and aromatic C), 163.61(C=O), 171.42 (C=O) ppm.

(4*S,5:4'*R**)-Spiro[3-(*p*-anisyl)-4-phenylisoxazoline-5,4'-(2'-phenyl)isoquinoline-1',3'-dione] (3ag):** Yield (62%); white solid; Mp175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, OCH_3), 5.21 (s, 4-H), 6.75-8.26 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.69 (OCH_3), 67.27 (C-4), 90.57 (C-5,4'), 114.53-161.65 (C-3 and aromatic C), 164.25 (C=O), 172.06 (C=O) ppm.

(5*R,4:4'*R**)-Spiro[3-(*p*-anisyl)-5-phenylisoxazoline-4,4'-(2'-phenyl)isoquinoline-1',3'-dione] (4ag):** Yield (20%); white solid; Mp 220 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, OCH_3), 6.29 (s, 5-H), 6.85-8.07 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.78 (OCH_3), 96.70 (C-5), 70.94 (C-4,4'), 114.64-161.81 (C-3 and aromatic C), 163.58 (C=O), 171.51 (C=O) ppm.

(4*S,5:4'*R**)-Spiro[3-(*p*-anisyl)-4-(*p*-tolyl)isoxazoline-5,4'-(2'-phenyl)isoquinoline-1',3'-dione] (3bg):** Yield (60%); orange solid; Mp 204 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, CH_3), 3.76 (s, OCH_3), 5.20 (s, 4-H), 6.73-8.25 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.56 (CH_3) 55.67 (OCH_3) 67.06 (C-4), 90.57 (C-5,4'), 114.47-161.43 (C-3 and aromatic C), 164.34 (C=O), 172.20 (C=O) ppm.

(5*R,4:4'*R**)-Spiro[3-(*p*-anisyl)-5-(*p*-tolyl)isoxazoline-4,4'-(2'-phenyl)isoquinoline-1',3'-dione] (4bg):** Yield (18%); colourless solid; Mp 227 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, CH_3) 3.80 (s, OCH_3), 6.25 (s, 5-H), 6.83-8.10 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.43 (CH_3) 55.79 (OCH_3), 96.93 (C-5), 70.92 (C-4,4'), 114.75-161.77 (C-3 and aromatic C), 163.83 (C=O), 171.58 (C=O) ppm.

(4*S,5:4'*R**)-Spiro[3-(*p*-anisyl)-4-(*p*-anisyl)isoxazoline-5,4'-(2'-phenyl)isoquinoline-1',3'-dione] (3cg):** Yield (62%); white solid; Mp 236 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, OCH_3), 3.79 (s, OCH_3), 5.18 (s, 4-H), 6.55-7.99 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.55 (OCH_3), 55.68 (OCH_3), 66.80 (C-4), 90.53(C-5,4'), 114.53-161.59 (C-3 and aromatic C), 164.31 (C=O), 172.14 (C=O) ppm. Anal. Calcd for $C_{31}H_{24}N_2O_5$: C, 73.80; H, 4.79; N, 5.55. Found: C, 73.75; H, 4.72; N, 5.50.

(5*R,4:4'*R**)-Spiro[3-(*p*-anisyl)-4-(*p*-anisyl)isoxazoline-4,4'-(2'-phenyl)isoquinoline-1',3'-dione] (4cg):** Yield (22%); orange solid; Mp 183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, OCH_3), 3.80 (s,

OCH_3), 6.21(s, 5-H), 6.65-8.10 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.56 (OCH_3), 55.75 (OCH_3), 96.83 (C-5), 70.92 (C-4,4'), 114.08-161.77 (C-3 and aromatic C), 163.62 (C=O), 171.57 (C=O) ppm.

(4*S,5:4'*R**)-Spiro[3-(*p*-anisyl)-4-(*p*-nitrophenyl)isoxazoline-5,4'-(2'-phenyl)isoquinoline-1',3'-dion] (3dg):** Yield (62%); dark brown solid; Mp 216 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, OCH_3), 5.20 (s, 4-H), 6.70-8.30 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.66 (s, OCH_3), 67.38 (C-4), 90.60 (C-5,4'), 114.50-161.71 (C-3 and aromatic C), 164.42 (C=O), 172.09 (C=O) ppm.

(5*R,4:4'*R**)-Spiro[3-(*p*-anisyl)-5-(*p*-nitrophenyl)isoxazoline-4,4'-(2'-phenyl)isoquinoline-1',3'-dione] (4dg):** Yield (25%); colourless solid; Mp 186 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, OCH_3), 6.27 (s, 5-H), 6.80-8.15 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.76 (s, OCH_3), 96.90 (C-5), 70.97 (C-4,4'), 114.72-161.90 (C-3 and aromatic C), 163.54 (C=O), 171.53 (C=O) ppm. Anal. Calcd for $C_{30}H_{21}N_3O_6$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.24; H, 3.98; N, 8.03.

ACKNOWLEDGEMENTS

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. The authors would like to thank Dr. Besma Hamdi (Laboratoire des Sciences de Matériaux et d'Environnement, Faculté des Sciences de Sfax, Tunisie) for XRD measurements.

REFERENCES

1. N. Uenver, T. Goezler, N. Walch, B. Goezler, and M. Hesse, *Phytochemistry*, 1999, 50, 1255; G. Grethe, 'Isoquinolines Part 1: In the series Chemistry of Heterocyclic Compounds Vol. 38', ed. by A. Weissberger and E. C. Taylor, Wiley, New York, 1981. pp. 1-4.
2. D. A. Carper, T. C. Hohman, and S. E. Old, *Biochim. Biophys. Acta*, 1995, 1246, 67; M. S. Malamas and T. C. Hohman, *J. Med. Chem.*, 1994, **37**, 2059.
3. J. P. Hoelck, W. Kampe, A. Mertens, B. Mueller-Bekmann, and K. Strein, Ger. Offen DE Pat.3410168 (*Chem. Abstr.*,1986, **104**, 50877).
4. V. M. Kisel, E. O. Kostyrko, and V. A. Kovtunenko, *Chem. Heterocycl. Compd.,* 2002, **38**, 1295; T. Yashiro, K. Yamada, and H. Shirai, *Chem. Pharm. Bull.*,1975, **23**, 2054; S. Chiavarelli, F. Rabagliati, and G. Settimj, *Gazz. Chim. Ital.*, 1960, **90**, 189; J. C. Gramain, S. Mavel, Y. Troin, D. Vallee-Goyet, *Tetrahedron*, 1991, **47**, 7301; S. S. Huybrechts and G. J. Hoornaert, *Synth. Commun.*,1981, **11**, 17.
5. L. Capuano and C. Wamprecht, *Liebigs Ann. Chem.,* 1986, **5**, 938; F. Ponticelli and P. Teedeschi,

Heterocycles, 1983, **20**, 1315; A. Bahloul, S. Kitane, and M. Soufiaoui, *J. Soc. Maroc. Chim.,* 1993, **2**, 12.

6. J. C. Gramain, Y. Troin, and D. Vallee, *J. Chem. Soc., Chem. Commun.*, 1981, **16**, 832; H. Kagi and K. Miescher, *Helv. Chim. Acta*, 1949, **32**, 2489.
7. M. Askri, N. Jegham, M. Rammah, K. Ciamala, K. M. Jobé, and J. Vebrel, *Heterocycles*, 2007, **71**, 289.
8. A. S. Bailey, A. P. Ledger, and N. R. D. Perkins, *J. Chem. Soc., C*, 1967, 323; H. Kubota, A. Kakefuda, H. Nagaoka, O. Yamamoto, K. Ikeda, M. Takeuchi, T. Shibanuma, and Y. Isomura, *Chem. Pharm. Bull.*, 1998, **46**, 242.
9. K. C. Liu, R. B. Shelton, and R. K. Howe, *J. Org. Chem.*, 1980, **45**, 3916; C. Grundman and R. Richter, *J. Org. Chem*., 1967, **32**, 2308; R. Huisgen and N. Mack, *Tetrahedron Lett.,* 1961, **2**, 583; R. H. Wiley and B. J. Wakefield, *J. Org. Chem.,* 1960, **25**, 546; Y. H. Chiang, *J. Org. Chem.,* 1971, **36**, 2146.
10. S. Manikandan, M. Shanmugasundarm, R. Raghunathan, and E. J. Padma Malar, *Heterocycles*, 2000, **53**, 579; R. Fihi, K. Ciamala, J. Vebrel, and N. Rodier, *Bull. Soc. Chim. Belg.,* 1995, **104**, 55.
11. D. E. Horning, G. Lacasse, and L. M. Muchowski, *Can. J. Chem.*, 1971, **49**, 246.