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Regiospecific Hetero Diels-Alder Synthesis of Furo[2,3-*g*] and Furo[3,2-*g*]quinoline-4,9-diones

Omar Cherkaoui, Pascal Nebois, Houda Fillion*

Laboratoire de Chimie Organique, Institut des Sciences Pharmaceutiques et Biologiques, Université Claude Bernard, Lyon I
8 avenue Rockefeller, 69373 Lyon Cedex 08, France. Fax : 78 77 71 58; e-mail : fillion@cismsun.univ-lyon1.fr

Monique Domard

Laboratoire de Chimie Analytique II, Institut des Sciences Pharmaceutiques et Biologiques, Université Claude Bernard, Lyon I
8, Avenue Rockefeller F-69373 Lyon Cedex 08, France

Bernard Fenet

Centre de RMN, Université Claude Bernard Lyon I, F-69622 Villeurbanne Cedex, France

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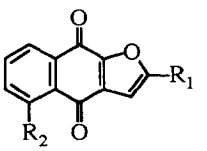
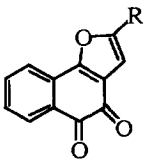
Abstract : Diels-Alder reactions of 5- or 6-bromobenzofuran-4,7-diones **7** or **10** towards azadienes **1** afford regiospecifically furo[2,3-*g*] or furo[3,2-*g*]quinoline-4,9-diones **3** or **4**. Assignment of the regioisomers, made by 2D NMR ^{1}H-^{13}C HMBC experiments, showed that the regiochemistry of the cycloadditions is under control of the bromine atom position. Calculations by the semiempirical method PM3 of the HOMO and LUMO orbital coefficients of azadienes **1** and quinones **2** indicated that the larger ones are situated at C-4 for **1** and C-5 for **2**.

Naturally occurring or synthetic naphtho[2,3-*b*]furan-4,9-diones **I** as well as naphtho[1,2-*b*]furan-4,5-diones **II** have shown significant *in vitro* cytotoxicity against KB cells.[1,2] More recently, some other derivatives of naphthofuranquinones were described for *in vitro* antiprotozoan activity against *Trypanosoma cruzi*.[3]



I

R_1 = COMe, CHOHMe; R_2 = H or OH

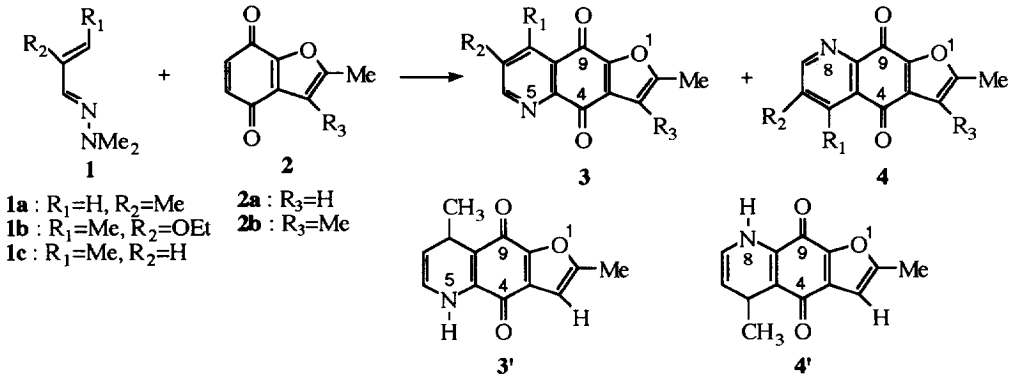


II

R = H, Me

In view to obtain aza analogues of **I** or **II** of potential antitumor or antiprotozoan activity, we planned to synthesize furoquinolinedione derivatives. So, furo[2,3-*f*]quinoline-4,5-diones were previously prepared by building the furan or the pyridine ring through [3+2] or [4+2] cycloadditions.[4] In continuation of our program aimed to develop hetero Diels-Alder routes to compounds having a pyridine nucleous annulated to benzofurandione, we need an efficient strategy to provide furo[2,3-*g*] and furo[3,2-*g*]quinoline-4,9-diones. Our first approach starts with benzofuran-4,7-diones **2a** or **2b** used in Diels-Alder reactions with α,β-unsaturated N,N-dimethylhydrazones **1**[5] (Scheme 1).

Scheme 1



RESULTS AND DISCUSSION

The [4+2] cycloadditions between azadienes **1a** or **1b** and quinones **2**, gave mixtures of furoquinolines **3** and **4** through spontaneous elimination of dimethylamine and oxidation. In contrast, cycloadditions of **1c** towards **2a** led to a mixture of the stable dihydro cycloadducts **3'** and **4'** (Table 1).

Table 1. Cycloadditions of azadienes **1** to benzofuran-4,7-diones **2**

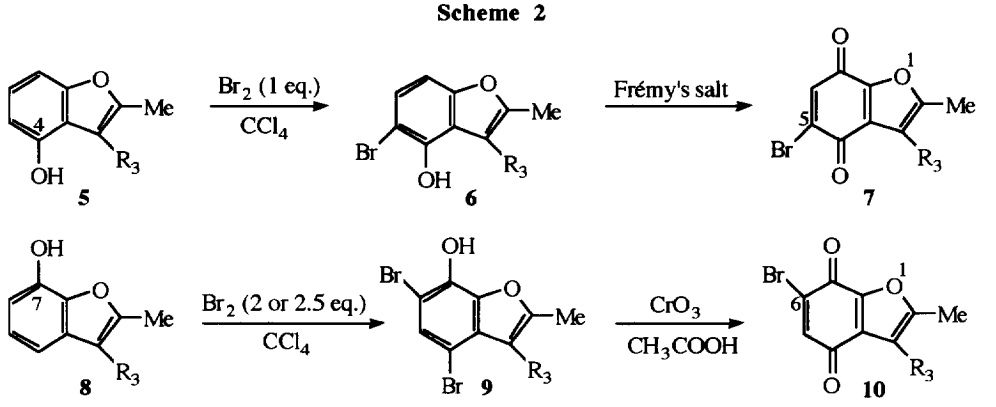
Entry	Azadiene (eq.)	Quinone	(Solvent, temp., reaction time)	Products	R_1	R_2	R_3	Yield (%)	Ratio* **3 / 4**
1	**1a** (1.5)	**2a**	EtOH, r.t., 3h	**3aa+4aa**	H	Me	H	98	27 / 73
2	**1a** (1.5)	**2b**	EtOH, r.t., 3h	**3ab+4ab**	H	Me	Me	97	8 / 92
3	**1b** (2)	**2a**	EtOH, r.t., 24h	**3ba+4ba**	Me	OEt	H	54	45 / 55
4	**1b** (2)	**2b**	EtOH, r.t., 24h	**3bb+4bb**	Me	OEt	Me	67	34 / 66
5	**1c** (1,5)	**2a**	Toluene, r.t., 24h	**3'+4'**	Me	H	H	47	12 / 88
6	**1c** (1,5)	**2b**	MeCN, reflux, 6h	**3cb+4cb**	Me	H	Me	38	33 /67

*Measured from the ^{1}H-NMR spectra.

A good regioselectivity was observed with azadienes **1a** and **1c** towards quinones **2b** and **2a** respectively (entries 2 and 5). But, separation of the regioisomers **3** and **4** or **3'** and **4'** failed. To obtain furoquinolinediones **3** or **4** regiospecifically, we turn our attention to the preparation and use of the unknown 5- or 6-bromobenzofuran-4,7-diones **7** or **10**. The presence of a bromine atom at C-5 or C-6 on these quinones was expected to afford regiospecificity.[6]

Bromobenzofurandiones **7** and **10** were prepared from the corresponding hydroxybenzofurans **5** or **8** according to Scheme 2. Treatment of 4-hydroxybenzofuran **5a** or **5b** with bromine (1eq.) in carbon tetrachloride gave the *o*-brominated derivatives **6a** or **6b** as single products in 65 and 76% yield respectively, while in the same conditions 7-hydroxybenzofuran **8a** or **8b** yielded a mixture of the corresponding *o*-bromophenol, *p*-bromophenol and the dibromo derivative **9a** or **9b**. Then, using respectively 2 or 2.5 eq. of bromine afforded exclusively **9a** or **9b** in excellent yields (95 and 86% respectively). Oxidation of **6** with Frémy's salt and **9** with chromic anhydride in glacial acetic acid, gave **7** and **10**.

Scheme 2



5a-10a: R_3=H **5b-10b**: R_3=Me

Cycloadditions of azadienes **1** to bromobenzofurandiones **7** or **10**, performed at room temperature in acetonitrile, afforded regiospecifically the corresponding furoquinolinediones **3** or **4** (Scheme 3 and Table 2). In most cases, better yields in compounds **3** and **4** were obtained by carrying out the Diels-Alder reactions in the presence of triethylamine or sodium hydrogenocarbonate. Such bases were used in order to trap hydrogen bromide evolved and to avoid further polymerization of azadienes.[7,8]

Scheme 3

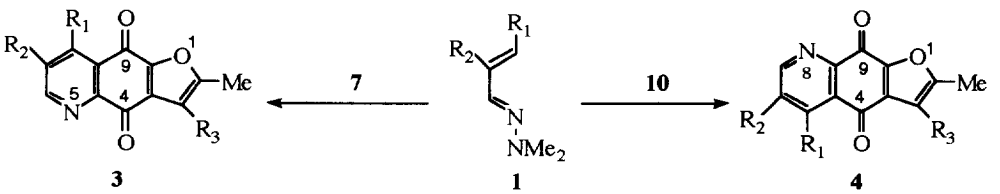
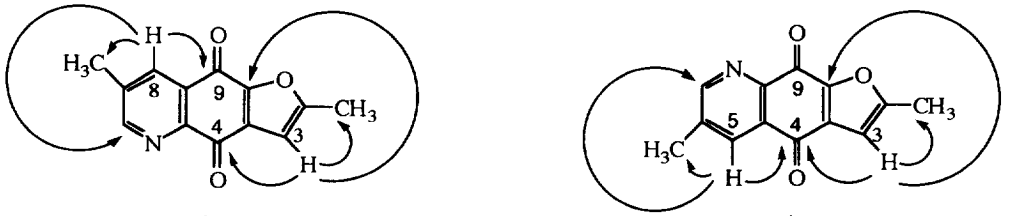


Table 2. Regiospecific cycloadditions of azadienes **1** to bromoquinones **7** or **10**. ^{1}H-NMR spectral data of R_1 and R_3 in furoquinoline **3** and **4** ($CDCl_3$, 300 MHz)

Azadiene (eq.)	Bromo-quinone	Base (eq.)	Conditions (temp., time)	Product	R_1	R_2	R_3	Yield (%)	δ ppm (R_1)	δ ppm (R_3)
1a (1.5)	**7a**	-	r.t., 2h	**3aa**	H	Me	H	87	8.32	6.70
1a (1.5)	**10a**	$NaHCO_3$ (2)	r.t., 1.5h	**4aa**	H	Me	H	90	8.26	6.63
1a (1.5)	**7b**	-	r.t., 3h	**3ab**	H	Me	Me	84	8.30	2.34
1a (1.5)	**10b**	-	r.t., 3h	**4ab**	H	Me	Me	85	8.24	2.31
1b (3)	**7a**	Et_3N (3)	r.t., 3h	**3ba**	Me	OEt	H	81	2.75	6.64
1b (3)	**10a**	Et_3N (3)	r.t., 6h	**4ba**	Me	OEt	H	82	2.72	6.59
1b (3)	**7b**	Et_3N (5)	r.t., 6h	**3bb**	Me	OEt	Me	82	2.75	2.31
1b (3)	**10b**	Et_3N (3)	r.t., 6h	**4bb**	Me	OEt	Me	86	2.71	2.29
1c (2)	**7a**	$NaHCO_3$ (2)	reflux, 6h	**3ca**	Me	H	H	65	2.89	6.67
1c (2)	**10a**	$NaHCO_3$ (2)	reflux, 6h	**4ca**	Me	H	H	52	2.85	6.61
1c (2)	**7b**	$NaHCO_3$ (2)	reflux, 6h	**3cb**	Me	H	Me	75	2.87	2.32
1c (2)	**10b**	$NaHCO_3$ (2)	reflux, 6h	**4cb**	Me	H	Me	69	2.85	2.30

Concerning the regiochemistry of the cycloadditions, opposite regioisomers were obtained from 6-bromobenzofuran-4,7-diones **10** comparatively to those formed from 5-bromobenzofuran-4,7-diones **7**. To explain the regiospecificity, it was assumed that the unbrominated carbon atom of these quinones was exclusively attacked by the nucleophilic end of azadienes. The regioisomeric furoquinolinediones **3** and **4** were identified from their ^{1}H-NMR spectra. Thus, the chemical shifts of R_1 and R_3 in the 1,5- regioisomers **3** are shifted to higher fields by 0.02 to 0.07 ppm comparatively to those of the 1,8- ones **4** (Table 2). Proof of the structures were made by 2D ^{1}H-^{13}C NMR HMBC correlations performed on **3aa** and **4aa** (Fig. 1). This technique let us to correlate the protons with the carbon atoms through ^{1}J, ^{2}J, ^{3}J and ^{4}J ^{1}H-^{13}C couplings. Concerning long range couplings, ^{3}J are larger than ^{2}J and ^{4}J in aromatic compounds. Thus, for compound **3aa**, ^{3}J couplings were observed for H-3/CH_3-2, H-3/C-4, H-3/C-9a, H-8/C-6, H-8/CH_3-7 and H-8/C-9 while the opposite regioisomer **4aa** gave ^{3}J couplings between H-3/CH_3-2, H-3/C-4, H-3/C-9a, H-5/C-4, H-5/CH_3-6 and H-5/C-7.



3aa **4aa**

Figure 1. Some selected ^{1}H-^{13}C HMBC correlations for **3aa** and **4aa**.

In order to better understand the behaviour of azadienes **1** in their Diels-Alder reactions towards quinones **2**, **7** and **10**, we calculated their respective HOMO and LUMO orbital coefficients by the semi-empirical method PM3.[9] Thus, the values given in Table 3 indicated that the larger coefficients were located at C-4 for azadienes **1** while they are at C-5 for quinones **2**. Furthermore, a substitution by the bromine atom at C-5 (quinones **7**) enhanced the orbital coefficients of C-6 but, the latter remained smaller than those of C-5.

Table 3. Orbital coefficients of azadienes **1** and benzofuran-4,7-diones **2**, **7** and **10**

Azadiene (HOMO)	N-1	C-4
1a	0.240	0.322
1b	0.301	0.408
1c	0.274	0.315
Benzofuran-4,7-dione (LUMO)	C-5	C-6
2a	0.365	0.344
2b	0.366	0.345
7a	0.378	0.371
7b	0.379	0.372
10a	0.390	0.358
10b	0.391	0.359

On the other hand, the presence of a bromine at C-6 (quinones **10**) increased the coefficients of C-5. Thus, the regiochemistry observed in the cycloadditions between azadienes **1** and quinones **2** or **10** agrees with the

calculations. Indeed, C-4 of **1** attacks preferentially or exclusively at C-5 of **2** or **10**. But, in the case of 5-bromoquinones **7**, the LUMO coefficients at C-5 and C-6 being very close, the bromine atom exerts a blocking effect. Thus, the nucleophilic end of **1** adds to the unbrominated carbon C-6.

CONCLUSION

This work describes an efficient way to reach regiospecifically two unusual heterocyclic ring systems through Diels-Alder reactions between 1-azadienes **1** and 5- or 6-bromobenzofuran-4,7-diones **7** or **10**. Concerning the cycloadditions of **1** towards quinones **2** or **10**, the regiochemistry observed agrees with HOMO and LUMO orbital coefficients. In the case of 5-bromoquinones **7**, the regiospecificity obtained may be explained by the orientational regiocontrol of the bromine atom.

EXPERIMENTAL SECTION

Melting points were taken in a capillary tube using a Büchi 510 apparatus and are corrected. IR spectra were performed on a Perkin-Elmer 1310 spectrophotometer. The ^{1}H-NMR spectra were recorded at 200 and 300 MHz on Bruker AC 200 and AM 300 spectrometers. For carrying out 2D ^{1}H-^{13}C HMBC spectra, 5 mg of compound **3aa** or **4aa** were dissolved at room temperature in 0.5 mL of $CDCl_3$. The HMBC technique was performed with gradients selection[10] which give very clean 2D matrix with very small T_1 noise. The J filter and transfer time for long range coupling were fixed respectively to 3.22 ms and 80 ms. The acquisition parameters were : AQ = 0.18 ms, SW2 = 2793 Hz, SW1 = 3586 Hz, NE = 512, NS = 48, relaxation delay D_1 = 1,5 s. Prior to the FFT, the signal was weighted by a none shifted sinbell in the two dimensions. The size of the final matrix was 1k.1k. Elemental analysis were made at the Centre de Microanalyse du CNRS at Solaize. Column chromatography was carried out with Matrex (60 Å, 35-70 µm) acidic silica gel. Preparative circular thin layer chromatography was performed with a Chromatotron Harrison Research apparatus using silica gel 60 PF 254 containing gypsum as the adsorbant. Coefficients of the molecular frontier orbitals were calculated from MOPAC of SYBYL program on an IBM Risk 6000 workstation. Azadienes **1a**,[11] **1b**,[4,12] **1c**,[12] 2,3-dimethylbenzo[*b*]furan-4,7-dione **2b**,[13] 4-Hydroxybenzofurans **5a**,[14] **5b**[15] and 7-hydroxy-2,3-dimethylbenzofuran **8b**[16] were prepared according to procedures described in the respective literature.

2-Methylbenzo[*b*]furan-4,7-dione 2a

Frémy's salt (1.35 g) was dissolved in 60 mL of water and 20 mL of a buffered aqueous solution of KH_2PO_4 (0.6 M). This solution was added at room temperature and under stirring to a solution of compound **5a** (0.3 g, 2.02 mmol) in 20 mL of ethanol. Then, the orange reaction mixture was stirred 1h at 0°C. The orange precipitate corresponding to quinone **2a** formed was recovered by filtration. Extraction of the filtrate with ether (2x50 mL) gave an additionnal fraction of **5a**. The crude product was purified by column chromatography on silica gel using a mixture of EtOAc/hexane : 1/4 as the eluent. Quinone **2a** was obtained as a yellow powder in 74 % yield, mp 148 °C (ethanol). IR (KBr): 1665 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm 6.65 (s, 2H, H-5 and H-6), 6.46 (q, 1H, J=0.6 Hz, H-3), 2.44 (d, 3H, J=0.6 Hz, CH_3-2). Anal. Calcd for $C_9H_6O_3$, 0.05 H_2O : C, 66.29; H, 3.77. Found: C, 66.32; H, 3.81.

7-Hydroxy-2-methylbenzo[*b*]furan 8a

Compound **8a** was prepared from 7-methoxy-2-methylbenzo[*b*]furan following a modified procedure to that described in the literature.[17] Iodine (6.14 g, 24.5 mmol) was added under stirring to a solution of

o-eugenol[18] (3.61 g, 22 mmol) in acetonitrile (60 mL). Stirring was maintained for 24h at room temperature and in the dark. Then, the reaction mixture was treated with DBU (10 mL, 66 mmol) in dichloromethane (60 mL) and heated to reflux for 6h. After cooling and extraction with chloroform, the organic phase was washed twice with 50 mL of $NaHSO_3$ and 30 mL of a saturated aqueous solution of sodium chloride. Evaporation of the solvent gave a residue which was purified by column chromatography on silica gel using EtOAc/hexane : 6 /1 as the eluent. 7-Methoxy-2-methylbenzo[*b*]furan was obtained in 65 % yield as an oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm 7.13 to 7.06 (m, 2H, H-4 and H-5), 6.73 (dd, 1H, J=6.8 and 1.6 Hz, H-6), 6.36 (q, 1H, J=1.5 Hz, H-3), 4.0 (s, 3H, OCH_3), 2.47 (d, 3H, J=1.5 Hz, CH_3-2).

A mixture of 7-methoxy-2-methylbenzo[*b*]furan (2g, 12.3 mmol) and pyridinium hydrochloride (4 g, 34.6 mmol) was heated to reflux for 1h. After cooling and neutralization with hydrochloric acid, the reaction mixture was extracted with 3x30 mL of ether. Evaporation of the solvent and distillation of the residue gave compound **8a** (1.5 g, 82%). $Eb_{3\ mm\ Hg}$ 90°C. IR (KBr): 3400 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm 7.07 to 7.02 (m, 2H, H-4 and H-5), 6.75 (dd, 1H, J=5.4 and 3.6 Hz, H-6), 6.37 (q, 1H, J=1.0 Hz, H-3), 5.30 (s, 1H, OH), 2.46 (d, 3H, J=1.0 Hz, CH_3-2). Anal. Calcd for $C_9H_8O_2$, 0.1 H_2O : C, 72.08; H, 5.51; O, 22.40. Found: C, 72.14; H, 5.43; O, 22.26.

Brominations of hydroxybenzofurans 5 or 8. General procedures

For bromination of 4-hydroxybenzofurans **5**, bromine (0.986 g, 6.1 mmol) in carbon tetrachloride (20 mL) was added dropwise at room temperature and under stirring to a solution of 6.1 mmol of **5** in 60 mL of the same solvent. Stirring was maintained for 3h until complete elimination of hydrogen bromide. After evaporation of the solvent, the corresponding *o*-bromophenol **6** was purified by column chromatography on silica gel using an appropriate eluent.

For bromination of 7-hydroxybenzofurans **8**, bromine (1.28 g, 8 mmol for **8a** or 1.61 g, 10.7 mmol for **8b**) in carbon tetrachloride (30 mL) was added dropwise at room temperature and under stirring to a solution of 4 mmol of **8** in 40 mL of the same solvent. Stirring was maintained for 4h. The corresponding dibromophenol **9** was purified as above with an appropriate eluent.

5-Bromo-4-hydroxy-2-methylbenzo[*b*]furan 6a

Eluent : CH_2Cl_2/hexane : 1/4. Grey solid, mp 74 °C (ethanol/water : 3/1). Yield 65%. IR (KBr): 3480, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm 7.24 (d, 1H, J=9.0 Hz, H-6), 6.92 (d, 1H, J=9.0 Hz, H-7), 6.47 (q, 1H, J=0.9 Hz, H-3), 5.69 (s, 1H, OH), 2.44 (d, 3H, J=0.9 Hz, CH_3-2). Anal. Calcd for $C_9H_7BrO_2$: C, 47.60; H, 3.10; O, 14.09. Found: C, 47.58; H, 3.11; O, 14.10.

5-Bromo-4-hydroxy-2,3-dimethylbenzo[*b*]furan 6b

Eluent : CH_2Cl_2/hexane : 1/8. White solid, mp 118 °C (hexane). Yield 76%. IR (KBr): 3480, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm 7.20 (d, 1H, J=8.7 Hz, H-6), 6.86 (d, 1H, J=8.7 Hz, H-7), 5.63 (broad signal, 1H, OH),2.33 (q, 3H, J=0.6 Hz, CH_3-2), 2.30 (q, 1H, J=0.6 Hz, CH_3-3). Anal. Calcd for $C_{10}H_9BrO_2$: C, 49.82; H, 3.76; Br, 33.14. Found: C, 49.85; H, 3.80; 32.86.

4,6-Dibromo-7-hydroxy-2-methylbenzo[*b*]furan 9a

Purified by recrystallization from methanol. White solid, mp 120 °C. Yield 95%. IR (KBr): 2260 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm 7.41 (s, 1H, H-5), 6.39 (q, 1H, J=1,0 Hz, H-3), 5.64 (broad signal, 1H,

OH), 2.47 (d, 3H, J=1,0 Hz, CH_3-2). Anal. Calcd for $C_9H_6Br_2O_2$: C, 35.33; H, 1.97. Found: C, 35.69; H, 2.10.

4,6-Dibromo-7-hydroxy-2,3-dimethylbenzo[*b*]furan 9b

Eluent : EtOAc/hexane : 1/4. Beige crystals, mp 140 °C (methanol). Yield 86%. IR (KBr): 3300 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ ppm 7.39 (s, 1H, H-5), 5.58 (s, 1H, OH), 2.37 (q, 3H, J=0.7 Hz, CH_3-2), 2.32 (q, 3H, J=0.7 Hz, CH_3-3). Anal. Calcd for $C_{10}H_8Br_2O_2$, 0.05 H_2O : C, 37.43; H, 2.54; Br, 49.80. Found: C, 37.62; H, 2.48, 49.55.

Oxidations of bromophenols 6 or 9. General procedures

To obtain 5-bromobenzofurandiones **7**, the following procedure was used. Compound **6** (1.5 mmol) in 40 mL of acetone was added dropwise and under stirring to a solution of 1.4 g of Frémy's salt in 60 mL of water and 20 mL of a buffered aqueous solution of KH_2PO_4 (0.6 M) previously cooled at 0°C. Then, the orange reaction mixture was stirred 1h at 0°C and 2h at room temperature. The orange precipitate of the corresponding 5-bromoquinone **7** formed was recovered by filtration. Extraction of the filtrate with ether (3x40 mL) gave an additionnal fraction of **7**. This crude product was purified by column chromatography on silica gel using an appropriate eluent.

To obtain 6-bromobenzofurandiones **10**, the following procedure was used. Compound **9** (1.5 mmol) was added under stirring to a solution, previously heated to reflux, of CrO_3 (0.47 g, 5.3 mmol) in 20 mL of acetic acid. In the case of **10a**, the reaction mixture was stirred at room temperature for 1h while in the case of **10b** stirring and heating were maintained for 30 min. After cooling, 20 mL of water were added and the mixture was extracted with ether (3x40 mL). Evaporation of the solvent gave the corresponding 6-bromoquinone **10** which was purified as above.

5-Bromo-2-methylbenzo[*b*]furan-4,7-dione 7a

Eluent : EtOAc/hexane : 1/5. Orange powder, mp 150 °C (AcOEt/hexane : 1/8). Yield 81%. IR (KBr): 1680, 1665 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ ppm 7.19 (s, 1H, H-6), 6.55 (q, 1H, J=1.0 Hz, H-3), 2.48 (d, 3H, J=1.0 Hz, CH_3-2). Anal. Calcd for $C_9H_5BrO_3$: C, 44.84; H, 2.09. Found: C, 45.25; H, 2.22.

5-Bromo-2,3-dimethylbenzo[*b*]furan-4,7-dione 7b

Eluent : EtOAc/hexane : 1/8. Orange powder, mp 148 °C (AcOEt/hexane : 1/8). Yield 75%. IR (KBr): 1680, 1670 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ ppm 7.16 (s, 1H, H-6), 2.38 (s, 3H, CH_3-2), 2.22 (s, 3H, CH_3-3). Anal. Calcd for $C_{10}H_7BrO_3$: C, 47.09; H, 2.76. Found: C, 47.38; H, 2.68.

6-Bromo-2-methylbenzo[*b*]furan-4,7-dione 10a

Eluent : EtOAc/hexane : 1/4. Orange powder, mp 170 °C (AcOEt/hexane : 1/6). Yield 65%. IR (KBr): 1670, 1660 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ ppm 7.17 (s, 1H, H-5), 6.48 (q, J=0.9 Hz, 1H, H-3), 2.49 (d, 3H, J=0.9 Hz, CH_3-2). Anal. Calcd for $C_9H_5BrO_3$: C, 44.80; H, 2.09; Br, 33.14. Found: C, 44.87; H, 2.02; Br, 33.04.

6-Bromo-2,3-dimethylbenzo[*b*]furan-4,7-dione 10b

Eluent : EtOAc/hexane : 1/5. Orange powder, mp 124 °C (AcOEt/hexane : 1/8). Yield 70%. IR (KBr): 1680, 1665 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ ppm 7.12 (s, 1H, H-5), 2.39 (q, 3H, J=0.6 Hz, CH_3-2),

2.20 (q, 3H, J=0.6 Hz, CH_3-3). Anal. Calcd for $C_{10}H_7BrO_3$: C, 47.09; H, 2.76; Br, 31.32. Found: C, 47.16; H, 2.92; Br, 31.49.

5,8-Dihydro-2,8-dimethylfuro[2,3-*g*]quinoline-4,9-dione 3' and 5,8-dihydro-2,5-dimethylfuro[3,2-g]quinoline-4,9-dione 4'

A solution of azadiene **1c** (0.209 g, 1.86 mmol) in 2 mL of anhydrous toluene was added dropwise to quinone **2a** (0.202 g, 1.24 mmol) in the same solvent (12 mL) at room temperature under stirring and nitrogen stream. At the end of the addition, stirring was maintained 24 h under an inert atmosphere. Then, the solvent was evaporated and the residue purified by preparative circular thin layer chromatography (hexane/acetone: 3/1). The mixture of the two unseparable regioisomers was obtained as a blue powder (0.134 g, 47%). IR (KBr): 3320, 1675, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm **3'**: 6.74 (s, 1H, NH), 6.36 (q, 1H, J=1.0 Hz, H-3), 6.14 (dd, 1H, J=7.6 and 4.4 Hz, H-6), 5.00 to 4.97 (m, 1H, H-7), 3.96 to 3.60 (m, 1H, H-8), 2.42 (d, 3H, J=1.0 Hz, CH_3-2), 1.16 (d, 3H, J=6.0 Hz, CH_3-8), **4'**: 6.75 (s, 1H, NH), 6.46 (q, 1H, J=0.8 Hz, H-3), 6.14 (dd, 1H, J=7.6 and 4.4 Hz, H-7), 5.00 to 4.94 (m, 1H, H-6), 3.69 to 3.60 (m, 1H, H-5), 2.46 (d, 3H, J=0.8 Hz, CH_3-2), 1.13 (d, 3H, J=6.4 Hz, CH_3-5). Anal. Calcd for $C_{13}H_{11}NO_3$, 0.4 H_2O : C, 66.04; H, 5.03; N, 5.92. Found: C, 65.86; H, 5.00; N, 5.88.

Cycloadditions to bromoquinones 7 and 10. General procedure

Data required in the following procedure (equivalent of azadiene and base, temperature, reaction time) are available in the Table 2. A solution of azadiene in 2 mL of anhydrous acetonitrile was added dropwise and under stirring to a mixture of the corresponding quinone **7** or **10** (0.5 mmol) and base in the same solvent (6 mL). At the end of the addition, stirring was maintained until completion of the reaction. Then, the solvent was evaporated and the yellow residue purified by preparative circular thin layer chromatography using an appropriate eluent.

2,7-Dimethylfuro[2,3-*g*]quinoline-4,9-dione 3aa

Eluent: CH_2Cl_2; mp 292 °C (EtOAc). Yield: 0.099 g, 87%. IR (KBr): 1680, 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm 8.82 (d, 1H, J=2.0 Hz, H-6), 8.32 (d, 1H, J=2.0 Hz, H-8), 6.70 (s, 1H, H-3), 2.54 (s, 3H, CH_3-2 or CH_3-7), 2.53 (s, 3H, CH_3-2 or CH_3-2); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ ppm 178.98 (CO-4), 172.15 (CO-9), 161.28 (C-2), 154.35 (C-6), 151.35 (C-9a), 146.74 (C-7), 138.43 (C-4a), 134.79 (C-8), 132.46 (C-3a), 129.11 (C-8a), 105.56 (C-3), 18.81 (CH_3-7), 14.21 (CH_3-2). Anal. Calcd for $C_{13}H_9NO_3$, 0.2 H_2O: C, 67.64; H, 4.10; N, 6.06. Found: C, 67.69; H, 3.99; N, 5.90.

2,6-Dimethylfuro[3,2-*g*]quinoline-4,9-dione 4aa

Eluent: CH_2Cl_2; mp 288 °C (EtOAc). Yield: 0.102 g, 90%. IR (KBr): 1675 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm 8.83 (d, 1H, J=2.3 Hz, H-7), 8.26 (d, 1H, J=2.3 Hz, H-5), 6.63 (q, 1H, J=1.0 Hz, H-3), 2.53 (1s and 1d, 6H, J=1.0 Hz, CH_3-6 and CH_3-2); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ ppm 179.83 (CO-4), 171.25 (CO-9), 161.19 (C-2), 154.75 (C-7), 152.10 (C-9a), 146.43 (C-6), 138.20 (C-8a), 134.79 (C-5), 131.62 (C-3a), 129.63 (C-4a), 104.92 (C-3), 18.81 (CH_3-6), 14.20 (CH_3-2). Anal. Calcd for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.16. Found: C, 68.71; H, 3.92; N, 6.24.

2,3,7-Trimethylfuro[2,3-*g*]quinoline-4,9-dione 3ab

Eluent: CH_2Cl_2; mp 205 °C (acetonitrile). Yield: 0.101 g, 84%. IR (KBr): 1680, 1670 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ ppm 8.80 (d, 1H, J=1.9 Hz, H-6), 8.30 (d, 1H, J=1.9 Hz, H-8), 2.52 (s, 3H, CH_3-7), 2.44 (s, 3H, CH_3-2), 2.34 (s, 3H, CH_3-3). Anal. Calcd for $C_{14}H_{11}NO_3$, 0.6 H_2O: C, 66.71; H, 4.87; N, 5.55. Found: C, 66.71; H, 4.97; N, 5.41.

2,3,6-Trimethylfuro[3,2-*g*]quinoline-4,9-dione 4ab

Eluent: CH_2Cl_2; mp 256 °C (acetonitrile). Yield: 0.103 g, 85%. IR (KBr): 1680, 1670 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ ppm 8.82 (d, 1H, J=2.0 Hz, H-7), 8.24 (d, 1H, J=2.0 Hz, H-5), 2.53 (s, 3H, CH_3-6), 2.44 (s, 3H, CH_3-2), 2.31 (s, 3H, CH_3-3). Anal. Calcd for $C_{14}H_{11}NO_3$, 0.8 H_2O: C, 65.77; H, 4.96; N, 5.47. Found: C, 65.86; H, 4.70; N, 5.36.

7-Ethoxy-2,8-dimethylfuro[2,3-*g*]quinoline-4,9-dione 3ba

Eluent: CH_2Cl_2/MeOH, 95/5; mp 274 °C (EtOAc). Yield: 0.110 g, 81%. IR (KBr): 1690, 1660 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ ppm 8.46 (s, 1H, H-6), 6.64 (s, 1H, H-3), 4.28 (q, 2H, J=7.0 Hz, $OC\underline{H}_2CH_3$), 2.75 (s, 3H, CH_3-8), 2.51 (s, 3H, CH_3-2), 1.53 (t, 3H, J=7.0 Hz, $OCH_2C\underline{H}_3$). Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.38; H, 4.74; N, 5.20.

6-Ethoxy-2,5-dimethylfuro[3,2-*g*]quinoline-4,9-dione 4ba

Eluent: CH_2Cl_2/MeOH, 95/5; mp 318 °C (EtOAc). Yield: 0.111 g, 82%. IR (KBr): 1670 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ ppm 8.48 (s, 1H, H-7), 6.59 (q, 1H, J=0.7 Hz, H-3), 4.29 (q, 2H, J=6.9 Hz, $OC\underline{H}_2CH_3$), 2.72 (s, 3H, CH_3-5), 2.51 (d, 3H, J=0.7 Hz, CH_3-2), 1.53 (t, 3H, J=6.9 Hz, $OCH_2C\underline{H}_3$). Anal. Calcd for $C_{15}H_{13}NO_4$, 0.25 H_2O : C, 65.33; H, 4.93; N, 5.08. Found: C, 65.10; H, 4.94; N, 5.40.

7-Ethoxy-2,3,8-trimethylfuro[2,3-*g*]quinoline-4,9-dione 3bb

Eluent: CH_2Cl_2/MeOH, 95/5; mp 304 °C (CH_2Cl_2/EtOH, 1/1). Yield: 0.117 g, 82%. IR (KBr): 1685, 1670 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ ppm 8.45 (s, 1H, H-6), 4.28 (q, 2H, J=7.0 Hz, $OC\underline{H}_2CH_3$), 2.75 (s, 3H, CH_3-8), 2.41 (s, 3H, CH_3-2), 2.31 (s, 3H, CH_3-3), 1.53 (t, 3H, J=7.0 Hz, $OCH_2C\underline{H}_3$). Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.34; H, 5.29; N, 4.91. Found: C, 67.04; H, 5.48; N, 4.96.

6-Ethoxy-2,3,5-trimethylfuro[3,2-*g*]quinoline-4,9-dione 4bb

Eluent: CH_2Cl_2/MeOH, 95/5; mp 258 °C (CH_2Cl_2/EtOH, 1/1). Yield: 0.123 g, 86%. IR (KBr): 1685, 1670 cm^{-1}. ^1H-NMR ($CDCl_3$, 200 MHz) δ ppm 8.47 (s, 1H, H-7), 4.28 (q, 2H, J=7,0 Hz, $OC\underline{H}_2CH_3$), 2.71 (s, 3H, CH_3-5), 2.41 (q, 3H, J=0.5 Hz, CH_3-2), 2.29 (q, 3H, J=0.5 Hz, CH_3-3), 1.53 (t, 3H, J=7,0 Hz, $OCH_2C\underline{H}_3$). Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.34; H, 5.29; N, 4.91. Found: C, 67.49; H, 5.27; N, 4.87.

2,8-Dimethylfuro[2,3-*g*]quinoline-4,9-dione 3ca

Eluent: CH_2Cl_2; mp 229 °C (acetonitrile). Yield: 0.074 g, 65%. IR (KBr): 1690, 1665 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ ppm 8.81 (d, 1H, J=4.9 Hz, H-6), 7.43 (d, 1H, J=4.9 Hz, H-7), 6.67 (s, 1H, H-3), 2.89 (s, 3H, CH_3-8), 2.53 (s, 3H, CH_3-2). Anal. Calcd for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.16. Found: C, 68.91; H, 4.06; N, 6.12.

2,5-Dimethylfuro[3,2-*g*]quinoline-4,9-dione 4ca

Eluent: CH_2Cl_2; mp 248 °C (acetonitrile). Yield: 0.059 g, 52%. IR (KBr): 1665 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ ppm 8.82 (d, 1H, J=4.9 Hz, H-7), 7.42 (d, 1H, J=4.9 Hz, H-6), 6.61 (q, 1H, J=0.6 Hz, H-3), 2.85 (s, 3H, CH_3-5), 2.54 (d, 3H, J=0.6 Hz, CH_3-2). Anal. Calcd for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.16. Found: C, 68.80; H, 3.88; N, 6.12.

2,3,8-Trimethylfuro[2,3-*g*]quinoline-4,9-dione 3cb

Eluent: CH_2Cl_2; mp 295 °C (acetone).Yield: 0.090 g, 75%. IR (KBr): 1685, 1665 cm^{-1}. ^1H-NMR ($CDCl_3$, 200 MHz) δ ppm 8.78 (d, 1H, J=4.9 Hz, H-6), 7.40 (d, 1H, J=4.9 Hz, H-7), 2.87 (s, 3H, CH_3-8), 2.42 (s, 3H, CH_3-2), 2.32 (s, 3H, CH_3-3). Anal. Calcd for $C_{14}H_{11}NO_3$, 0.1 H_2O : C, 69.18; H, 4.64; N, 5.78. Found: C, 69.11; H, 4.56; N, 5.71.

2,3,5-Trimethylfuro[3,2-*g*]quinoline-4,9-dione 4cb

Eluent: CH_2Cl_2; mp 238 °C (acetone).Yield: 0.083 g, 69%. IR (KBr): 1680, 1670 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ ppm 8.80 (d, 1H, J=4.9 Hz, H-7), 7.40 (d, 1H, J=4.9 Hz, H-6), 2.85 (s, 3H, CH_3-5), 2,43 (s, 3H, CH_3-2), 2,30 (s, 3H, CH_3-3). Anal. Calcd for $C_{14}H_{11}NO_3$, 0.1 H_2O : C, 69.18; H, 4.64; N, 5.78. Found: C, 69.06; H, 4.65; N, 5.73.

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