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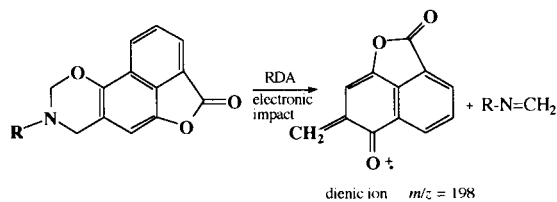
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7-Arylidene-2*H*,6*H*-naphtho[1,8-*bc*]furan-2,6-diones **3** were prepared by a retro-Diels-Alder reaction of the corresponding dihydro 1,3-oxazines **2** or in a one pot synthesis from 6-hydroxy-2*H*-naphtho[1,8-*bc*]furan-2-one **1**. Their *E* configuration was established from the chemical shift's values of the vinylic proton and by ¹H nmr NOE difference spectroscopy. Cycloadditions of **3b** upon styrene or stilbene were catalyzed by boron trifluoride etherate. The cycloadducts were obtained with the relative *trans* configuration.

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In a previous work, we described the synthesis and the antitumor or antifungal activities of a series of *N*-substituted [1] or 7,8,9-substituted-7,8-dihydro-4*H*,9*H*-furo[2',3',4':4,4a,5]naphth-[2,1-*e*][1,3]oxazin-4-ones **2** [2] [3]. Furthermore, we reported [1] that the *N*-substituted derivatives gave by mass spectrometry, under electronic impact, a retro-Diels-Alder fragmentation leading to a dienic ion *m/z* = 198 and the corresponding imine as dienophile (Scheme 1).

Scheme 1



On the other hand, Mannich bases of phenols are known to be thermally unstable and to decompose to the respective secondary amine and *o*-quinone methide [4] [5]. Our attempts to prepare and isolate the corresponding *o*-quinone methide (Scheme 1) by a thermal retro-Diels-Alder (RDA) reaction from the *N*-substituted dihydrofuronaphthoxazine derivatives failed, probably due to a dimer or trimer formation [6]. Then, we expected that a substitution of the ethylenic double bond by an aromatic group, may stabilize this structure and offer a new possibility for synthetic developments.

In the present work, we describe the synthesis and the usefulness in the Diels-Alder reaction of arylidenyl naphthofuran diones **3**. Thus, compounds **3** were successfully prepared by a retro-Diels-Alder reaction from the 7,8,9-substituted furonaphthoxazines **2** or in a one pot synthesis starting from 6-hydroxy-2*H*-naphtho[1,8-*bc*]furan-2-one **1** [7] [8], *t*-butylamine and two equivalents of various aromatic aldehydes (Table 1).

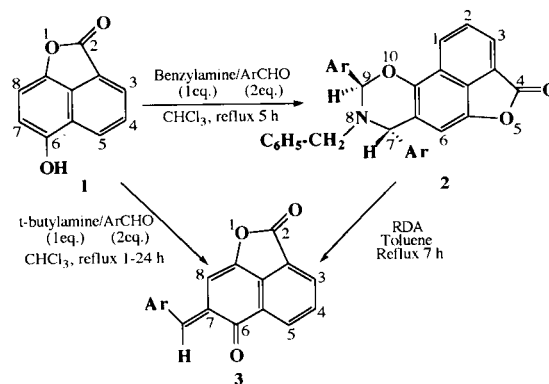


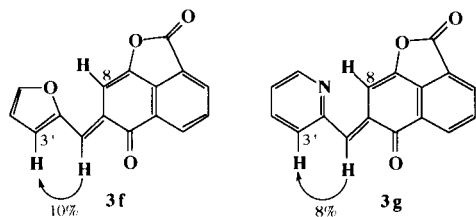
Table 1

No.	Ar	¹ H nmr chemical shift (CDCl ₃ , δ ppm)	
		H vinylic	H-8
3a	C ₆ H ₅	8.27	7.05
3b	<i>p</i> -Cl-phenyl	8.20	6.99
3c	<i>p</i> -CH ₃ -phenyl	8.27	7.10
3d	<i>p</i> -NO ₂ -phenyl	8.22	6.90
3e	<i>p</i> -CH ₃ O-phenyl	8.24	7.13
3f	2'-furyl	7.83	7.75
3g	2'-pyridyl	7.99	8.67
3h	3'-pyridyl	8.18	6.91

All compounds **3** were obtained stereospecifically as a single stereoisomer. Their diastereoisomeric purity and *E* configuration were corroborated by ¹H nmr spectroscopy at 300 MHz. In these derivatives, the chemical shift's values of H-8 are in the range of 6.9 to 7.34 ppm excepted when the aryl substituent is 2'-furyl (**3f**) or 2'-pyridyl (**3g**), while those of the vinylic proton are deshielded by more than 1 ppm (Table 1). Deshielding of the latter is in good agreement with an *E* configuration, because this proton is under the anisotropic effect of the carbonyl group. Similar values of chemical shifts have been reported in the literature for the stereoisomers of 5-arylidenehydantoin [9], 3-arylidenebenzofuranones [10], 3-arylidenechromanones

[11] and 2-arylidencyclanones [12] in which the vinylic proton is *cis* to the carbonyl. The stereochemistry of compounds **3f** and **3g** was conclusively demonstrated by means of nuclear Overhauser effect difference spectroscopy. Irradiation of the vinylic proton gave only a ¹H NOEDIFF enhancement on H-3' (**3f**:10%; **3g**:8%). On the other hand, not any response was observed by irradiation of H-8. Deshielding of H-8 in **3f** and **3g** can be accommodated by a conformation in which this proton is very close to the heteroatom of the furyl or pyridyl substituent (Scheme 2).

Scheme 2



When trapped with alkenes, *o*-quinone methides underwent Diels-Alder addition giving rise to chromane derivatives [5] [6]. However, the yields remained poor. Heating the heterodiene **3b** with styrene or stilbene under reflux of toluene for several hours, only traces of compounds **4** were detected. These observations led us to check if a Lewis acid catalysis of the [4+2] cycloadditions would ameliorate them. Indeed, compounds **4** were obtained with moderate to excellent yield (40-90%) in the presence of one equivalent of boron trifluoride etherate (Table 2).

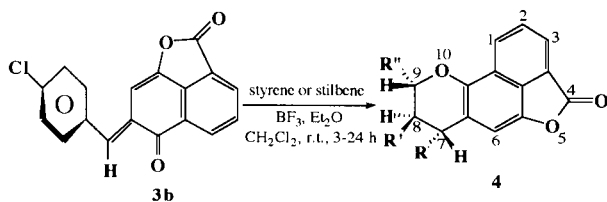


Table 2

No.	R	R'	R''
4a	<i>p</i> -Cl-C ₆ H ₄	C ₆ H ₅	H
4b	<i>p</i> -Cl-C ₆ H ₄	C ₆ H ₅	C ₆ H ₅

Considering the regio- and stereochemistry of **4a**, formation of a single regioisomer, the 7,8-substituted derivative, can be explained on the assumption that heterodiene **3b** reacts in its polar form [13]. Furthermore, the *J*-value (10.58 Hz) of the doublet at 5.34 ppm, confirms a relative *trans* configuration. This result indicates that the cycloaddition seems to be thermodynamically controlled. *Cis*- or *trans*-stilbene were indifferently used for the synthesis of **4b** which was obtained with a relative *trans,trans* configuration. This stereochemistry can be explained by a

possible isomerization of *cis*-stilbene catalysed by the Lewis acid.

EXPERIMENTAL

Melting points were measured on a Büchi apparatus (capillary tube). The infra-red spectra were performed on a Perkin-Elmer 1310 spectrophotometer. The ¹H nmr spectra were recorded at 300 MHz on a Bruker AM 300 Spectrometer. Elemental analysis were made at the Centre de Microanalyse du CNRS at Solaise, Lyon. Liquid aldehydes, *t*-butylamine, solvents and boron trifluoride etherate are freshly distilled before use.

Synthesis of the (*E*)-7-Arylidene-2*H*,6*H*-naphtho[1,8-*bc*]furan-2,6-diones **3**.

(*E*)-7-*p*-Chlorobenzylidene-2*H*,6*H*-naphtho[1,8-*bc*]furan-2,6-dione (**3b**).

Method A.

A solution of the oxazine **2** (Ar = *p*-chlorophenyl) [**3**] (0.269 g, 0.5 mmole) in anhydrous toluene (20 ml) was heated at reflux for 7 hours. A yellow precipitate of compound **3b** was formed by cooling the mixture. It was recovered and recrystallized from benzene. This compound was obtained in 56% yield, mp = 288°; ir (potassium bromide): ν cm⁻¹ 1810, 1665 (CO); ¹H nmr (deuterated chloroform): δ ppm 8.35 (doublet, H-5, 1H, *J* = 7.2 Hz), 8.2 (singlet, H vinyl, 1H), 8.17 (doublet, H-3, 1H, *J* = 7.5 Hz), 7.76 (doublet of doublet, H-4, 1H, *J* = 7.2 and 7.5 Hz), 7.49 to 7.3 (multiplet, H arom, 4H), 6.99 (singlet, H-8, 1H).

Anal. Calcd. for C₁₈H₉O₃Cl: C, 70.03; H, 2.94; Cl, 11.48. Found: C, 69.82; H, 2.92; Cl, 11.61.

Method B.

A solution of *p*-chlorobenzaldehyde (0.281 g, 2 mmole) in anhydrous dichloromethane (70 ml) was cooled in an ice bath. Then, *t*-butylamine (0.73 g, 1 mmole) was added and the resulting mixture was stirred at 0° for 30 minutes. Then, compound **1** [**8**] (0.186 g, 1 mmole) in dichloromethane (10 ml) was added and the reaction mixture was heated to reflux for 24 hours. Removing of the solvent and addition of methanol (10 ml) gave compound **3b** as a yellow precipitate. It was recovered and recrystallized from benzene. This compound was obtained in 80% yield.

(*E*)-7-Benzylidene-2*H*,6*H*-naphtho[1,8-*bc*]furan-2,6-dione (**3a**).

This compound was prepared according to method B. Compound **3a** was recrystallized from benzene/hexane (2:8). It was obtained in 51% yield, mp = 185°; ir (potassium bromide): ν cm⁻¹ 1790, 1650 (CO); ¹H nmr (deuterated chloroform): δ ppm 8.34 (doublet, H-5, 1H, *J* = 7.6 Hz), 8.27 (singlet, H vinyl, 1H), 8.15 (doublet, H-3, 1H, *J* = 7.5 Hz), 7.74 (doublet of doublet, H-4, 1H, *J* = 7.5 and 7.6 Hz), 7.57 to 7.46 (multiplet, H arom, 5H), 7.05 (singlet, H-8, 1H).

Anal. Calcd. for C₁₈H₁₀O₃: C, 78.82; H, 3.67. Found: C, 78.73; H, 3.55.

(*E*)-7-*p*-Methylbenzylidene-2*H*,6*H*-naphtho[1,8-*bc*]furan-2,6-dione (**3c**).

This compound was prepared according to method B. The reaction mixture was heated at reflux for 24 hours. Compound **3c** was recrystallized from benzene/hexane (2:3). It was obtained in 38% yield, mp = 244°; ir (potassium bromide): ν cm⁻¹ 1780,

1650 (CO); ¹H nmr (deuterated chloroform): δ ppm 8.36 (doublet, H-5, 1H, J = 7.6 Hz), 8.27 (singlet, H vinyl, 1H), 8.15 (doublet, H-3, 1H, J = 7.6), 7.74 (doublet of doublet, H-4, 1H, J = 7.6 Hz), 7.48 (doublet, H arom, 2H, J = 8.1 Hz), 7.31 (doublet, H arom, 2H, J = 8.1 Hz), 7.1 (singlet, H-8, 1H), 2.44 (singlet, CH₃, 3H).

Anal. Calcd. for C₁₉H₁₂O₃: C, 79.16; H, 4.20. Found: C, 79.00; H, 4.02.

(*E*)-7-*p*-Nitrobenzylidene-2*H*,6*H*-naphtho[1,8-*bc*]furan-2,6-dione (**3d**).

Method A.

The oxazine **2** (Ar = *p*-nitrophenyl) [**2**] was treated as for **3b**. Then, the reaction mixture was heated to reflux for 7 hours. Compound **3d** was purified by column chromatography on silica gel using dichloromethane/methanol (99:1) as the eluent. It was obtained in 70% yield, mp = 275°; ir (potassium bromide): ν cm⁻¹ 1810, 1665 (CO); ¹H nmr (deuterated chloroform): δ ppm 8.37 to 8.34 (multiplet, H-5 and H arom, 3H), 8.22 (singlet, H vinyl 1H), 8.18 (doublet, H-3, 1H, J = 7.6 Hz), 7.8 (doublet of doublet, H-4, 1H, J = 7.6 Hz), 7.7 (doublet, H arom, 2H, J = 8.2 Hz), 6.9 (singlet, H-8, 1H).

Anal. Calcd. for C₁₈H₉NO₅: C, 67.71; H, 2.84; N, 4.39. Found: C, 67.88; H, 2.98; N, 4.57.

Method B.

The reaction mixture was heated to reflux for 8 hours. Compound **3d** was purified as in method A. It was obtained in 70% yield.

(*E*)-7-*p*-Methoxybenzylidene-2*H*,6*H*-naphtho[1,8-*bc*]furan-2,6-dione (**3e**).

This compound was prepared according to method B. The reaction mixture was heated to reflux for 24 hours. Compound **3e** was purified by column chromatography on silica gel using ethyl acetate/hexane (2:3) as the eluent. It was obtained in 15% yield, mp = 185°; ir (potassium bromide): ν cm⁻¹ 1810, 1665, (CO); ¹H nmr (deuterated chloroform): δ ppm 8.35 (doublet, H-5, 1H, J = 7.7 Hz), 8.24 (singlet, H vinyl, 1H), 8.14 (doublet, H-3, 1H, J = 7.5 Hz), 7.74 (doublet of doublet, H-4, 1H, J = 7.5 and 7.7 Hz), 7.58 (doublet, H arom, 2H, J = 8.5 Hz), 7.13 (singlet, H-8, 1H), 7.02 (doublet, H arom, 2H, J = 8.5 Hz), 3.9 (singlet, CH₃, 3H).

Anal. Calcd. for C₁₉H₁₂O₄·1 H₂O: C, 70.81; H, 4.38. Found: C, 70.96; H, 4.10.

(*E*)-7-(2'-Furylidene)-2*H*,6*H*-naphtho[1,8-*bc*]furan-2,6-dione (**3f**).

This compound was prepared according to method B. The reaction mixture was heated to reflux for 5 hours. Compound **3f** was recrystallized from benzene/hexane (2:3). It was obtained in 70% yield, mp = 210°; ir (potassium bromide): ν cm⁻¹ 1790, 1665 (CO); ¹H nmr (deuterated chloroform): δ ppm 8.34 (doublet, H-5, 1H, J = 7.6 Hz), 8.14 (doublet, H-3, 1H, J = 7.5 Hz), 7.83 (singlet, H vinyl, 1H), 7.75 to 7.69 (multiplet, H-4, H-8 and H-5', 3H), 7.02 (doublet, H-3', 1H, J = 3.5 Hz), 6.63 (multiplet, H-4', 1H).

Anal. Calcd. for C₁₆H₈O₄·0.33 H₂O: C, 71.13; H, 3.21. Found: C, 71.08; H, 3.18.

(*E*)-7-(2'-Pyridylidene)-2*H*,6*H*-naphtho[1,8-*bc*]furan-2,6-dione (**3g**).

This compound was prepared according to method B. The reaction mixture was heated to reflux for 1 hour. Compound **3g** was recrystallized from dichloromethane. It was obtained in 50%

yield, mp = 246°; ir (potassium bromide): ν cm⁻¹ 1790, 1670 (CO); ¹H nmr (deuterated chloroform): δ ppm 8.81 (multiplet, H-6', 1H), 8.67 (singlet, H-8, 1H), 8.32 (doublet, H-5, 1H, J = 7.6 Hz), 8.15 (doublet, H-3, 1H, J = 7.6 Hz), 7.99 (singlet, H vinyl, 1H), 7.82 to 7.71 (multiplet, H-4 and H-5', 2H), 7.6 (doublet, H-3', 1H, J = 8 Hz), 7.32 (multiplet, H-4', 1H).

Anal. Calcd. for C₁₇H₉O₃N: C, 74.18; H, 3.29; N, 5.09. Found: C, 73.86; H, 3.30; N, 5.06.

(*E*)-7-(3'-Pyridylidene)-2*H*,6*H*-naphtho[1,8-*bc*]furan-2,6-dione (**3h**).

This compound was prepared according to method B. The reaction mixture was heated to reflux for 7 hours. Compound **3h** was recrystallized from benzene/hexane (8:2). It was obtained in 38% yield, mp = 228°; ir (potassium bromide): ν cm⁻¹ 1790, 1670 (CO); ¹H nmr (deuterated chloroform): δ ppm 8.81 (singlet, H-6', 1H), 8.68 (doublet, H-2', 1H, J = 3.5 Hz), 8.36 (doublet, H-5, 1H, J = 7.6 Hz), 8.19 (singlet, H vinyl, 1H), 8.18 (doublet, H-3, 1H, J = 7.6 Hz), 7.88 (doublet, H-4', 1H, J = 7.9 Hz), 7.78 (doublet of doublet, H-4, 1H, J = 7.6 Hz), 7.46 (doublet of doublet, H-3', 1H, J = 3.5 and 7.9 Hz), 6.95 (singlet, H-8, 1H).

Anal. Calcd. for C₁₇H₉O₃N: C, 74.18; H, 3.30; N, 5.09. Found: C, 74.46; H, 3.59; N, 4.72.

Synthesis of the 7,8 (or 7,8,9)-Substituted-7,8-dihydro-4*H*,9*H*-furo[2',4':4,4a,5]naphtho[2,1-*e*]pyran-4-ones **4**.

trans-7-*p*-Chlorophenyl-8-phenyl-7,8-dihydro-4*H*,9*H*-furo[2',4':4,4a,5]naphtho[2,1-*e*]pyran-4-one (**4a**).

A mixture of **3b** (0.154 g, 0.5 mmole) in dichloromethane (50 ml) and boron trifluoride etherate (0.062 ml, 0.5 mmole) was stirred at room temperature for 30 minutes. Then, styrene (0.057 ml, 0.5 mmole) was added and stirring was continued for 3 hours.

Removing dichloromethane and addition of methanol (10 ml), gave a yellow precipitate of compound **4a**. It was recovered and recrystallized from benzene/hexane (2:8). Compound **4a** was obtained in 90% yield, mp = 165°; ir (potassium bromide): ν cm⁻¹ 1785 (CO); ¹H nmr (deuterated chloroform): δ ppm 8.37 (doublet, H-1, 1H, J = 8 Hz), 8.12 (doublet, H-3, 1H, J = 7 Hz), 7.78 (doublet of doublet, H-2, 1H, J = 7 and 8 Hz), 7.57 to 7.36 (multiplet, H arom, 5H), 7.31 (doublet, H arom, 2H, J = 8.3 Hz), 7.16 (doublet, H arom, 2H, J = 8.3 Hz), 6.55 (singlet, H-6, 1H), 5.34 (doublet, H-7, 1H, J = 10.5 Hz), 4.56 to 4.50 (multiplet, H-8, 1H), 2.62 to 2.55 (multiplet, H-9 *cis*, 1H), 2.36 to 2.24 (multiplet, H-9 *trans*, 1H).

Anal. Calcd. for C₂₆H₁₇O₃Cl: C, 75.64; H, 4.15; Cl, 8.59. Found: C, 75.53; H, 4.31; Cl, 8.17.

trans,trans-7-*p*-Chlorophenyl-8,9-diphenyl-7,8-dihydro-4*H*,9*H*-furo[2',4':4,4a,5]naphtho[2,1-*e*]pyran-4-one (**4b**).

Cis or *trans*-stilbene were used. The reaction mixture was heated to reflux for 24 hours.

Compound **4b** was recrystallized from benzene/hexane (1:1). It was obtained in 40% yield, mp = 295°; ir (potassium bromide): ν cm⁻¹ 1780 (CO); ¹H nmr (deuterated chloroform): δ ppm 8.35 (doublet, H-1, 1H, J = 8 Hz), 8.13 (doublet, H-3, 1H, J = 7 Hz), 7.77 (doublet of doublet, H-2, 1H, J = 7 and 8 Hz), 7.26 to 7.22 (multiplet, H arom, 5H), 7.14 to 7.07 (multiplet, H arom, 5H), 6.88 to 6.81 (multiplet, H arom, 4H), 6.54 (singlet, H-6, 1H), 5.37 (doublet, H-7, 1H, J = 10.4 Hz), 4.66 (doublet, H-9, 1H, J = 10.7 Hz), 3.32 (doublet of doublet, H-8, 1H, J = 10.4 and 10.7 Hz).

Anal. Calcd. for C₃₂H₂₁O₃Cl: C, 78.60; H, 4.33; Cl, 7.25. Found: C, 78.45; H, 4.31; Cl, 7.47.

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