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2-Ethoxybut-2-enal N,N-dimethylhydrazone: A Useful Reagent for the Synthesis of Furo[2,3-*f*]quinoline-4,5-diones

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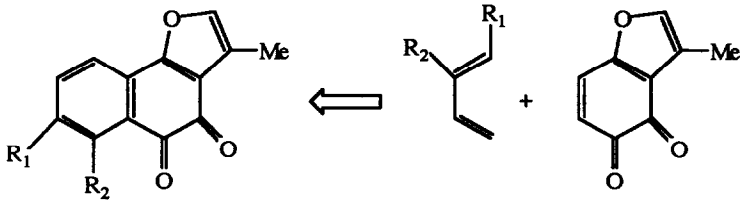
Abstract: The reactions of 2-ethoxybut-2-enal N,N-dimethylhydrazone with quinoline-5,8-diones or benzo[1,2-*b*]furan-4,5-diones through a [3+2] process or a [4+2] cycloaddition offer two efficient and regiospecific routes to substituted furo[2,3-*f*]quinoline-4,5-diones. Assignement of the structure and the regiochemistry of the Diels-Alder products is made by 1D ^{1}H NOE DIFF and 2D ^{1}H-^{13}C HMBC NMR experiments.

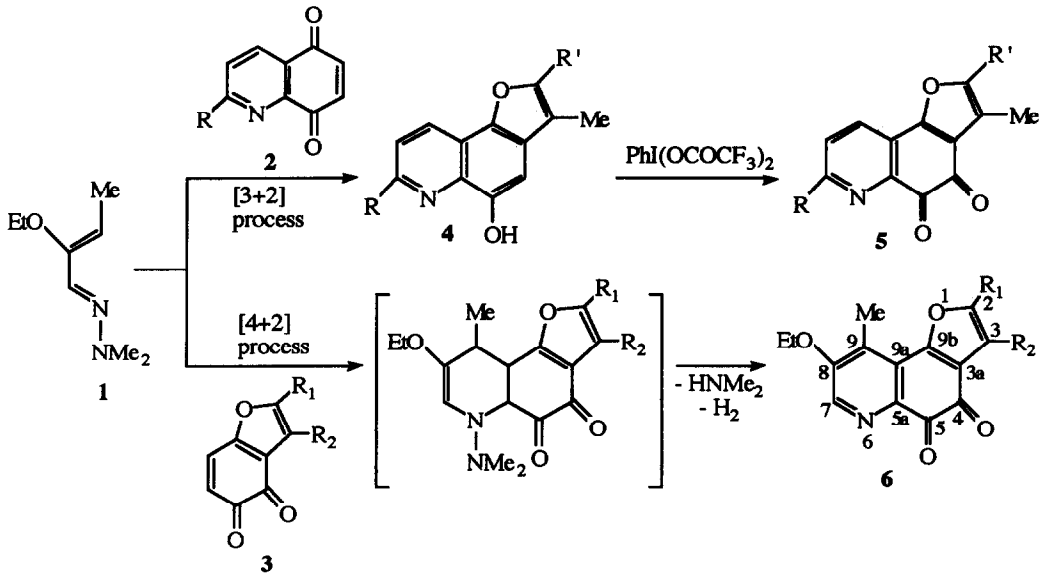
The naphtho[1,2-*b*]furan-4,5-dione skeleton is a chromophore present in naturally occuring quinones such as tanshinones[1] and phytoalexins.[2] Some of these derivatives exhibit a significant cytotoxic activity *in vitro* against KB cells .[3,4] The syntheses of this furoquinone **I** and tanshinones were also described.[5] More recently, Snyder *et al.* reported a total synthesis strategy for **I** and tanshinones, using 3-methyl benzofuran-4,5-dione as a dienophile in a [4+2] cycloaddition.[6]



I : $R_1 = R_2 = H$

In view to obtain aza analogues of **I** of potential antitumor activity, we planned to investigate the ability of 2-ethoxybut-2-enal N,N-dimethylhydrazone to provide with benzofuran-4,5-diones a such skeleton. Indeed, since 1-azadienes were shown to participate in Diels-Alder reactions,[7,8] their cycloadditions towards *o*-quinones have not yet been described. We report, in the present work, two routes to this furoquinoline-4,5-dione skeleton. First, we describe the oxidation of the previously prepared furoquinolines **4**[9] into the furoquinoline diones **5** and then, we develop the synthesis of compounds **6** through a [4+2] cycloaddition of azadiene **1** with *o*-quinones **3** according to Scheme 1.

Scheme 1



2a : R = H **4a** : R = H, R' = CH=N-NMe$_2$ **4c, 5c** : R = H, R' = CN

2b : R = Me **4b** : R = Me, R' = CH=N-NMe$_2$ **4d, 5d** : R = Me, R' = CN

3a, 6a : R_1 = H, R_2 = Me **3b, 6b** : R_1 = H, R_2 = Et **3c, 6c** : R_1, R_2 = -(CH$_2$)$_4$-

RESULTS AND DISCUSSION

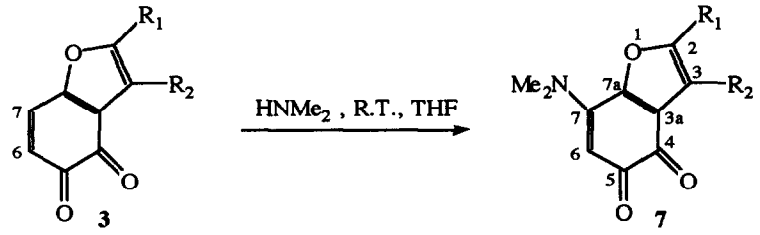
Oxidation of a phenolic group into *o*-quinone was previously performed by means of potassium nitrosodisulfonate[5a] or iodoxybenzene in the presence of acetic acid.[10] Furthermore, 1,4-naphthoquinones or 5,8-azanaphthoquinones were prepared from the corresponding 1-hydroxy naphthalenes or 5-hydroxy azanaphthalenes by the use of phenyliodonium bis(trifluoroacetate) (PIFA)[11] while phenyliodonium diacetate (PIDA) was successfully employed to obtain *p*-benzoquinones or *o*-benzoquinones from 1,4- or 1,2-diphenols.[12] In order to oxidize the phenolic group of **4** into the corresponding *o*-quinones **5**, the hydrazone function of **4a** and **4b** was converted to a cyano group by treatment with magnesium monoperoxyphtalate hexahydrate (MMPP) according to a known procedure.[13] Oxidation of **4c** and **4d** into the corresponding *o*-quinones by Fremy's salt failed, but was successfully performed with PIFA. Thus, *o*-quinones **5c** and **5d** were prepared in 78 % and 98 % respectively.

The Diels-Alder reaction of 3-methyl-4,5-benzofurandione **3a** with reactive 1,3-dienes such as 1-acetoxy-1,3-butadiene, 1-trimethylsilyloxy-1,3-butadiene or cyclopentadiene was reported by Snyder *et al.*[6a] to proceed in good to excellent yields. Furthermore, most of the tetra or dihydro adducts, detected by NMR, were found to aromatize under ambient conditions or upon chromatography on silica gel. The [4+2] cycloadditions of the activated azadiene **1** with *o*-quinones **3** were performed at room temperature in THF. The primary adducts or the dihydro derivatives were not isolated. But, the stable furoquinoline diones **6** precipitate in large amounts from the reaction mixture after spontaneous elimination of dimethylamine and aromatization. In contrast with the

cycloaddition of methacrolein N,N-dimethylhydrazone towards naphthoquinone, where the oxidation step consumes some dienophile used in excess,[7a] three equivalents of azadiene **1** were necessary in order to diminish the nucleophilic addition of the liberated dimethylamine upon the starting quinones (Scheme 2). Indeed, the use of a less amount of **1** (1.5 eq.) or an excess of the quinones **3** led to poorer yields in compounds **6** (38 % and 20 % respectively).

When the [4+2] cycloadditions were carried out at air, the N,N-dimethylamino benzofuran diones **7** were isolated in the respective yields: **7a**: 11, **7b**: 34 and **7c**: 33 %. Our attempts to eliminate dimethylamine by an intense nitrogen bubbling through the reaction mixture did not improve the cycloadditions but decreased largely the formation of the aminoquinone **7c** where only traces were identified by TLC. The structure of compounds **7** was confirmed by comparison of their physical and spectral data with those of authenthic samples prepared through a direct addition of dimethylamine on quinones **3** according to Scheme 2

Scheme 2



3a, **7a**: R_1 = H, R_2 = Me ; **3b**, **7b**: R_1 = H, R_2 = Et ; **3c**, **7c**: R_1, R_2 = -$(CH_2)_4$-

The ^{1}H-NMR spectral data of all compounds **4**, **5** and **6** exhibit close chemical shifts for common protons (see the Table).

Table. ^{1}H-NMR spectral data of compounds **4**, **5** and **6**.

Compound	H-7	H-2	CH_3-CH_2O	CH_3-CH_2	CH_3-9	CH_3-3	CH_3-CH_2O	CH_3-CH_2
4c	9.00	/	/	/	/	2.46	/	/
4d	/	/	/	/	/	2.45	/	/
5c	8.82	/	/	/	/	2.50	/	/
5d	/	/	/	/	/	2.42	/	/
6a	8.24	7.38	4.29	/	2.59	2.31	1.52	/
6b	8.26	7.39	4.30	2.77	2.60	/	1.53	1.26
6c	8.20	/	4.28	/	/	/	1.52	/

The structure determination of furoquinoline diones **6** and assignment of the NMR proton and carbon signals were made by 1D ^{1}H-NOE DIFF and 2D ^{1}H-^{13}C HMBC techniques performed on **6a**. In the latter, the

^1J couplings ^1H-^{13}C let us to determine the primary, secondary and tertiary carbons. Then, the ^2J and ^3J ^1H-^{13}C couplings allow to assign almost of all the quaternary carbons except C-3, C-3a and C-4, C-5. Moreover, the regiochemistry of the [4+2] cycloadditions was confirmed by the NOE DIFF experiment. Thus, an irradiation of the methyl group at C-9 shows interactions with H-2 and the methylene and methyl of the ethoxyl group while irradiation of H-2 gives a response on the methyl at C-3. This assignement of the regiochemistry agrees also with the prediction of the frontier orbital theory.

CONCLUSION

This work describes the ability of 2-ethoxybut-2-enal N,N-dimethylhydrazone to provide either with quinoline-5,8-diones or with benzofuran-4,5-diones, the furoquinoline-4,5-dione structure through a [3+2] and [4+2] processes respectively. The regiospecificity of these pathways offers two attractive routes to aza analogues of naturally occuring *o*-quinones. Moreover, it describes for the first time the Diels-Alder reaction of a 1-azadiene towards benzofuran-4,5-diones.

EXPERIMENTAL SECTION

All NMR spectra were recorded on a Bruker AM 300 (300 MHz) with tetramethylsilane as an internal standard. For performing 1D ^{13}C and 2D ^1H-^{13}C HMBC spectra, 10mg of compound **6a** were dissolved at 110°C in 0.5 ml of DMSO-d_6. The details of the recording were those given in reference.[9b] IR spectra were obtained on a Perkin-Elmer 1310 spectrophotometer. Elemental analyses were performed at the Service Central de Microanalyse du CNRS (Solaise). Melting points were determined with a Büchi 510 apparatus and are corrected. Thin-layer chromatography analyses (TLC) were performed on aluminium sheets precoated with silica gel 60 F_{254} (Merck). Column chromatography was carried out with Matrex (60 Å, 35-70 μm) silica gel. Preparative circular thin layer (2 mm) chromatography was made with a Chromatotron Harrison Research apparatus using silica gel 60 PF_{254} (Merck) containing gypsum as the adsorbant.

Solvents were freshly distilled before use. *o*-Quinone **3a**[6b] was prepared according to the procedure described in the literature.

2-Ethoxybut-2-enal N,N-dimethylhydrazone 1[14]

Azadiene **1** was prepared following a modified procedure of that described by Severin et *al.*[14] from crotonaldehyde N,N-dimethylhydrazone (12.8 g, 0.11 mmol) and bromine (10 ml). After the usual work-up and evaporation of solvent under vacuum at room temperature, 3-bromo-2-ethoxybutanal N,N-dimethylhydrazone was obtained as a brown oil. This intermediate was not isolated, but dissolved in absolute ethanol (100 ml) and added to a solution of sodium ethanolate (prepared from 3 g Na and 150 ml EtOH). The reaction mixture was then treated as described in reference.[14] Azadiene **1** was obtained after distillation under reduced pressure as an E+Z mixture in a ratio of 70:30. The geometrical assignment is not made. Yield % : 51; Eb_{3mmHg} : 57-59 °C; ^1H-NMR (300 MHz, $CDCl_3$) δ ppm 6.68 (s, 1H, H-2), 5.11 (q, 1H, J=7.2 Hz, H-4), 3.92 (q, 2H, J=7.1 Hz, CH_2), 2.81 (s, 6H, $(CH_3)_2N$), 1.71 (d, 3H, J=7.2 Hz, CH_3), 1.26, (t, 3H, J=7.1 Hz, CH_3) and 6.95 (s, 1H, H-2), 4.79 (q, 1H, J=7.2 Hz, H-4), 3.79 (q, 2H, J=7 Hz, CH_2), 2.90 (s, 6H,

$(CH_3)_2N$), 1.73 (d, 3H, J=7.2 Hz, CH_3), 1.33, (t, 3H, J=7 Hz, CH_3), respectively major and minor isomers. Azadiene **1** is stored at -20 °C for about 3 weeks.

2-Cyano-5-hydroxy-3-methylfuro[2,3-*f*]quinoline 4c

A solution of hydrazone **4a**[9b] (0.269 g, 1 mmol) in 2 ml of methanol was added under stirring to magnesium monoperoxyphtalate hexahydrate (1.224 g, 2.5 mmol) in the same solvent (8 ml) cooled to 0°C. At the end of the addition (5 min), stirring was maintained 5 min at 0°C. Then dichloromethane (25 ml) and water (25 ml) were added. The organic layer was washed twice with a saturated aqueous solution (25 ml) of sodium chloride. The solution was dried over magnesium sulfate and evaporated under vacuum. The yellow solid obtained was cristallized from ethanol to yield **4c** (0.204 g, 90%), M.p. 219°C; IR (KBr) ν 3360 (OH), 2220 (CN) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ ppm 9.90 (s, 1H, OH), 9.0 (dd, 1H, J=4.3 and 1.5 Hz, H-7), 8.71 (dd, 1H, J=8.3 and 1.5 Hz, H-9), 7.78 (dd, 1H, J=8.3 and 4.3 Hz, H-8), 7.27 (s, 1H, H-4), 2.46 (s, 3H, CH_3-3); Anal. Calcd. for $C_{13}H_8N_2O_2$, 0.1 H_2O: C, 69.08; H, 3.61; N, 12.39. Found: C, 69.09; H, 3.59; N, 12.11.

2-Cyano-5-hydroxy-3,7-dimethylfuro[2,3-*f*]quinoline 4d

Following the procedure used to prepare **4c**, compound **4d** was obtained from **4b**[9b] as a yellow powder (0.209 g, 88%). M.p. 224°C; IR (KBr) ν 3380 (OH), 2230 (CN) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ ppm 9.52 (s, 1H, OH), 8.58 (d, 1H, J=8.4 Hz, H-9), 7.65 (d, 1H, J=8.4 Hz, H-8), 7.25 (s, 1H, H-4), 2.76 (s, 3H, CH_3-7), 2.45 (s, 3H, CH_3-3); Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.62; H, 4.29; N, 11.81.

2-Cyano-4,5-dihydro-3-methylfuro[2,3-*f*]quinoline-4,5-dione 5c

A solution of nitrile **4c** (0.336 g, 1.5 mmol) in 9.3 ml of acetonitrile and 4.7 ml of water was added at -10 °C under stirring to phenyliodonium bis(trifluoroacetate) (1.5 g, 3.75 mmol) in 18 ml of the same mixture of solvents. At the end of the addition (15 min), dichloromethane (50 ml) was added. The organic layer was neutralized by a saturated aqueous solution of sodium hydrogen carbonate and washed with water. The solution was dried over magnesium sulfate and evaporated under vacuum. The residue was purified by column chromatography (hexane/AcOEt: 1/1) and gave **5c** as a red powder (0.280 g, 78%). M.p. 221°C; IR (KBr) ν 2220 (CN), 1715 (w.), 1680 (s.), and 1665 (w.) (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ ppm 8.82 (dd, 1H, J=4.7 and 1.4 Hz, H-7), 8.31 (dd, 1H, J=7.8 and 1.4 Hz, H-9), 7.75 (dd, 1H, J=7.8 and 4.7 Hz, H-8), 2.50 (s, 3H, CH_3-3); Anal. Calcd. for $C_{13}H_6N_2O_3$: C, 65.55; H, 2.53; N, 11.76. Found: C, 65.32; H, 2.73; N, 11.53.

2-Cyano-4,5-dihydro-3,7-dimethylfuro[2,3-*f*]quinoline-4,5-dione 5d

A solution of nitrile **4d** (0.357 g, 1.5 mmol) in 9.3 ml of acetonitrile and 4.7 ml of water was added at 0 °C under stirring to phenyliodonium bis(trifluoroacetate) (1.5 g, 3.75 mmol) in 18 ml of the same mixture of solvents. After the usual work-up, compound **5d** was obtained as a red powder (0.370 g, 98%). M.p. 217°C; IR (KBr) ν 2230 (CN), 1710 (w.), 1680 (s.) and 1660 (w.) (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ ppm 8.20 (d, 1H, J=8 Hz, H-9), 7.63 (d, 1H, J=8 Hz, H-8), 2.65 (s, 3H, CH_3-7), 2.42 (s, 3H, CH_3-3);

Anal. Calcd. for $C_{14}H_8N_2O_3$, 0.1 H_2O: C, 65.71; H, 3.23; N, 10.94. Found: C, 65.72; H, 3.29; N, 10.87.

3-Ethyl-4,5-dihydrobenzo[1,2-*b*]furan-4,5-dione 3b

Following the procedure used to prepare **3a**,[6b] compound **3b** was obtained from 0.329 g (2.03 mmol) of the corresponding phenolic derivative[15] as an orange powder (0.315 g, 89%). M.p. 101°C; IR (KBr) ν 1690 and 1660 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 7.28 (br s, 1H, H-2), 7.25 (d, 1H, J=9.8 Hz, H-7), 6.17 (d, 1H, J=9.8 Hz, H-6), 2.68 (dq, 2H, J=7.4 and 1.1 Hz, CH_2), 1.23 (t, 3H, J=7.4 Hz, CH_3). The poor stability of **3b** could not permit a satisfactory elemental analysis.

4,5-dihydro-2,3-tetramethylenebenzo[1,2-*b*]furan-4,5-dione 3c

Following the procedure used to prepare **3a**,[6b] compound **3c** was obtained from 0.382 g (2.03 mmol) of the corresponding phenolic derivative[15] as a red powder (0.327 g, 80%). M.p. 136°C; IR (KBr) ν 1690 and 1660 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 7.20 (d, 1H, J=10.2 Hz, H-7), 6.03 (d, 1H, J=10.2 Hz, H-6), 2.77-2.61 (m, 4H, $2CH_2$), 1.90-1.70 (m, 4H, $2CH_2$). The poor stability of **3c** could not permit a satisfactory elemental analysis.

8-Ethoxy-4,5-dihydro-3,9-dimethylfuro[2,3-*f*]quinoline-4,5-dione 6a

A solution of azadiene **1** (0.937 g, 6 mmol) in 9 ml of THF was added to *o*-quinone **3a** (0.324 g, 2 mmol) in the same solvent (50 ml) at room temperature under stirring. At the end of the addition (15 min) stirring was maintained 3 h. Then, the orange solid formed (**6a**) was filtered under vacuum. The filtrate was evaporated and the residue was purified by preparative circular thin layer chromatography (CH_2Cl_2/MeOH: 95/5). Then, an additional quantity of product was obtained. The fractions of **6a** were collected and recrystallized from acetonitrile. Yield: 0.336 g, 62%. M.p. 249°C; IR (KBr) ν 1700 (w.), 1680 (s.) and 1655 (w.) (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 8.24 (s, 1H, H-7), 7.38 (q, 1H, J=0.8 Hz, H-2), 4.29 (q, 2H, 6.9 Hz, $CH_3C\underline{H}_2O$), 2.59 (s, 3H, CH_3-9), 2.31 (d, 3H, J=0.8 Hz, CH_3-3), 1.52 (t, 3H, 6.9 Hz, $C\underline{H}_3CH_2O$); ^{13}C NMR (DMSO-d_6, 300 MHz) δ ppm 177.62 (CO-4 or CO-5), 174.66 (CO-4 or CO-5), 158.65 (C-9b), 155.69 (C-8), 142.59 (C-2), 138.45 (C-5a), 133.31 (C-7), 129.63 (C-9), 125.21 (C-9a), 121.64 (C-3 or C-3a), 119.85 (C-3 or C-3a), 64.92 ($CH_3\underline{C}H_2O$), 13.94 ($\underline{C}H_3CH_2O$), 11.25 (CH_3-9), 7.67 (CH_3-3); Anal. Calcd. for $C_{15}H_{13}NO_4$, 0.3 H_2O: C, 65.12; H, 4.95; N, 5.06. Found: C, 64.86; H, 4.80; N, 5.32.

8-Ethoxy-3-ethyl-4,5-dihydro-9-methylfuro[2,3-*f*]quinoline-4,5-dione 6b

Following the procedure used to prepare **6a**, compound **6b** was obtained from **3b** as an orange powder (0.228 g, 40%). M.p. 257°C (acetonitrile); IR (KBr): ν 1700 (w.), 1680 (s.)and 1655 (w.) (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 8.26 (s,1H, H-7), 7.39 (s, 1H, H-2), 4.3 (q, 2H, 6.9 Hz, $CH_3C\underline{H}_2O$), 2.77 (q, 2H, J=7.4 Hz, $CH_3C\underline{H}_2$-3), 2.60 (s, 3H, CH_3-9), 1.53 (t, 3H, J=6.9 Hz, $C\underline{H}_3CH_2O$), 1.26 (t, 3H, 7.4 Hz, $C\underline{H}_3CH_2$-3); Anal. Calcd. for $C_{16}H_{15}NO_4$, 0.7 H_2O: C, 64.51; H, 5.54; N, 4.70. Found: C, 64.49; H, 5.17; N, 4.91.

8-Ethoxy-4,5-dihydro-9-methyl-2,3-tetramethylenefuro[2,3-*f*]quinoline-4,5-dione 6c

Following the procedure used to prepare **6a**, compound **6c** was obtained from **3c** (0.156 g, 0.77 mmol) as orange needles (0.13 g, 54%). M.p. 260°C (acetonitrile); IR (KBr): ν 1700 (w.), 1675 (s.) and 1660 (w.) (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 8.20 (s,1H, H-7), 4.28 (q, 2H, 7 Hz, $CH_3\underline{CH_2}O$), 2.76-2.68 (m, 4H, $2CH_2$), 2.56 (s, 3H, CH_3-9), 1.93-1.76 (m, 4H, $2CH_2$), 1.53 (t, 3H, 7 Hz, $\underline{CH_3}CH_2O$); Anal. Calcd. for $C_{18}H_{17}NO_4$, H_2O: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.88; H, 5.65; N, 4.04.

4,5-Dihydro-3-methyl-7-N,N-dimethylaminobenzo[1,2-*b*]furan-4,5-dione 7a

Dimethylamine (0.5 ml) was added to *o*-quinone **3a** (0.324 g, 2 mmol) in THF (40 ml) at room temperature under stirring. At the end of the addition (5 min) the solution was evaporated under vacuum and the residue purified by preparative circular thin layer chromatography (CH_2Cl_2/MeOH: 95/5) to give **7a** as a purpurine powder which was recrystallized from AcOEt. Yield: 0.328 g, 80 %. M.p. 201C° ; IR (KBr): ν 1685 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 7.33 (br s, 1H, H-2), 5.35 (s, 1H, H-6), 3.35 (s, 6H, $N(CH_3)_2$), 2.26 (s, 3H, CH_3); Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.51; H, 5.40; N, 6.88.

3-Ethyl-4,5-dihydro-7-N,N-dimethylaminobenzo[1,2-*b*]furan-4,5-dione 7b

Following the procedure used to prepare **7a**, compound **7b** was obtained from **3b** as a purpurine powder (0.219 g, 50%). M.p. 187C° (AcOEt); IR (KBr): ν 1680 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 7.35 (br s, 1H, H-2), 5.38 (s, 1H, H-6), 3.37 (s, 6H, $N(CH_3)_2$), 2.73 (dq, 2H, J=7.5 and (Hz, CH_2), 1.22 (t, 3H, J=7.5 Hz, CH_3); Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.67; H, 5.81; N, 6.48.

4,5-Dihydro-7-N,N-dimethylamino-2,3-tetramethylenebenzo[1,2-*b*]furan-4,5-dione 7c

Following the procedure used to prepare **7a**, compound **7c** was obtained from **3c** (0.1 g, 0.48 mmol) as a purpurine powder (0.098 g, 83%). M.p. 194°C; IR (KBr): ν 1680 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 5.34 (s, 1H, H-6), 3.37 (s, 6H, $N(CH_3)_2$), 2.77-2.65 (m, 4H, $2CH_2$), 1.95-1.74 (m, 4H, $2CH_2$). Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.36; H, 6.22; N, 5.75.

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