Reactions of 3-Oxo-2,3-dihydrobenzofuran with Alkyl 2-Cyano-3-alkoxypropenoate and Alkyl 2-Alkoxycarbonyl-3-alkoxypropenoate. Synthesis of Pyran Derivatives

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3-Oxo-2,3-dihydrobenzofuran reacted with ethyl 2-cyano-3-ethoxypropenoate, methyl 2-cyano-3-methoxypropenoate affording compounds **3** (2-(2-cyano-2-alkoxycarbonylvinyl)-3-hydroxybenzofuran) obtained as a mixture of *Z* + *E* isomers. Methyl 2-methoxycarbonyl-3-methoxypropenoate gave compound **4**. Malonic compounds added on 2-dimethylaminomethylene-3-oxo-2,3-dihydrobenzofuran **6** for giving compound **3** or 2-oxo-3-methoxycarbonyl-2*H*-pyrano[3,2-*b*]benzofuran **8**. Compound **8** was also obtained by heating compound **4** in xylene.

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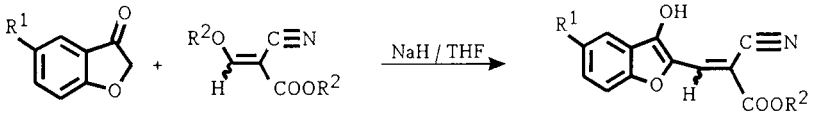
In our research program on the reactivity of heterocyclic ketones like 1-acetyl-3-oxo-2,3-dihydroindole [1-3] or 3-oxo-2,3-dihydrobenzofuran we have shown that the reaction of aldolization with aromatic aldehydes is very mild. The reactivity of the 2-position of 3-oxo-2,3-dihydrobenzofuran or 1-acetyl-3-oxo-2,3-dihydroindole [4] was examined towards alkyl 2-cyano-3-alkoxypropenoate and alkyl 2-alkoxycarbonyl-3-alkoxypropenoate. 4-Chromanones and 4-homochromanones directly gave, with these reagents, compounds having the pyrano structure like in the compound 2-oxo-3-ethoxycarbonyl-2*H*,5*H*-pyrano[3,2-*c*]benzopyran [5,6]; tetralones also gave similar pyrano compounds [7]. In the view of the well-known pharmacological interest of this class of compounds [8] we thought it worthwhile to develop their synthesis.

Condensation of 3-oxo-2,3-dihydrobenzofuran **1a** with methyl 2-cyano-3-methoxypropenoate **2a** (*E* + *Z* mixture) or ethyl 2-cyano-3-ethoxypropenoate (*E* + *Z* mixture) **2b** afforded respectively compound **3a** and **3b**; the reactions were performed in the presence of 1 or 2 equivalents of sodium hydride in THF at reflux or room temperature; cyclization to compounds having the pyrano ring was not observed even when 2 equivalents of sodium hydride were used as reported for chromanones [5-6]. Compounds **3a** and **3b** could also be obtained using potassium carbonate in dimethylformamide instead of sodium hydride.

Methyl 2-methoxycarbonyl-3-methoxypropenoate with compound **1a** afforded compound **4a** having a keto ethylene structure with the ester groups not conjugated with the ethylenec bond, contrary to compounds **3**. Compound

Figure 1A



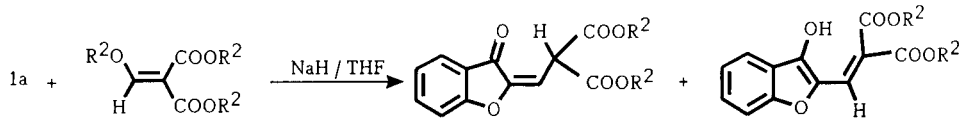
1 2 3

1a $R^1 = H$
1c $R^1 = Cl$

2a $R^2 = CH_3$
2b $R^2 = C_2H_5$

	R^1	R^2
3a	H	CH_3
3b	H	C_2H_5
3c	Cl	CH_3

Figure 1B



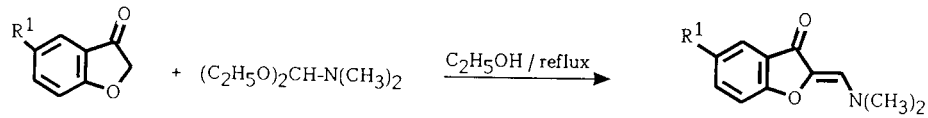
4 3

$R^2 = CH_3, C_2H_5$

4a $R^2 = CH_3$
4b $R^2 = C_2H_5$

3d $R^2 = C_2H_5$

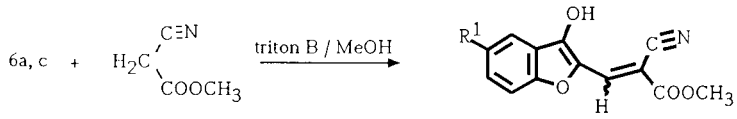
Figure 2A



1a $R^1 = H$
1c $R^1 = Cl$

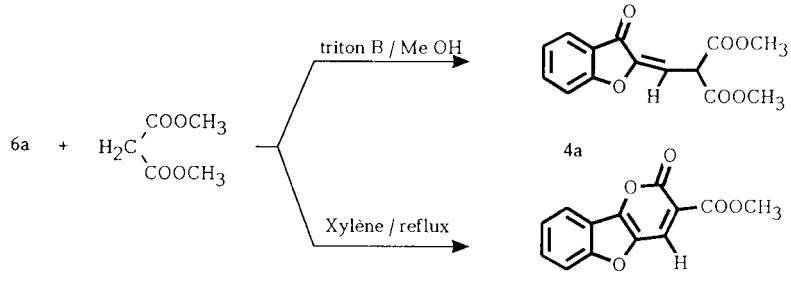
6a $R^1 = H$
6c $R^1 = Cl$

Figure 2B



3a $R^1 = H$
3c $R^1 = Cl$

Figure 2C



4a was obtained as a mixture of *Z* + *E* isomers where the *Z* isomer is predominant (90%). With ethyl 2-ethoxycarbonyl-3-ethoxypropenoate a mixture of compounds **3d** and **4b** was obtained where **4b** is largely predominant (90%) as the *Z* isomer (90%); nevertheless a very slow cristallization (1 month) from diethyl ether of the crude oil afforded **3d** in 30% yield.

Another route to compound **3** was to react *N,N*-dimethylformamide diethylacetal [9] with compound **1a** for giving 2-dimethylaminomethylene-3-oxo-2,3-dihydrobenzofuran **6a**. Compound **6a** reacted with ethyl cyanoacetate in the presence of a base, Triton B in methanol, giving compound **3a** (identical to the compound obtained when methyl cyanoacetate was used, due to a *trans* esterification). 5-Chloro-3-oxo-2,3-dihydrobenzofuran with dimethylformamide diethylacetal gave compound **6c**, which afforded compound **3c** with methyl cyanoacetate. Compound **4a** was similarly obtained from dimethyl malonate and compound **6a**.

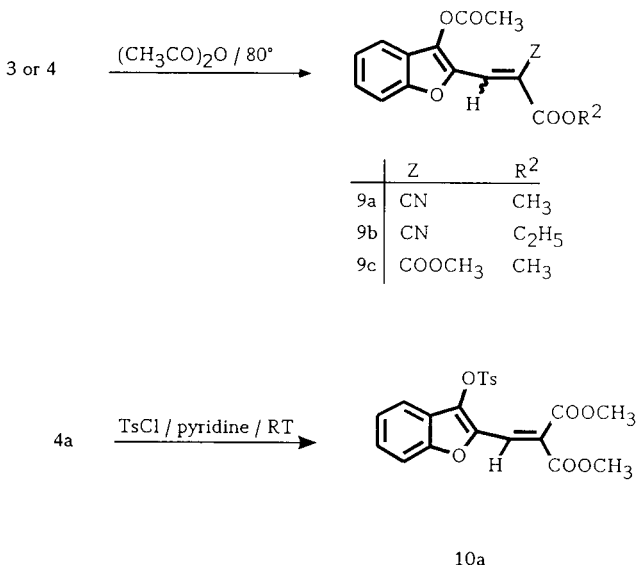
Nevertheless pyran **8** was obtained by heating compound **6a** with an excess of dimethyl malonate [10] at 140° or by heating compound **4a** in xylene at reflux.

Compound **8** or **4a** heated in ethanol in the presence of tetraethyl orthotitanate [11] gave the same compound **4b** resulting of the opening of the lactone with esterification. Heating compound **8** in methanol with a drop of concentrated sulfuric acid afforded compound **4a**.

In order to confirm the structure of compounds **3** they were aceytlated by acetic anhydride at 80° giving compounds **9**. Compound **4a** gave also compound **9c** under the same conditions. Compound **10a** was obtained by the reaction of *p*-toluenesulfonyl chloride with compound **4a** at room temperature in dichloromethane in the presence of pyridine.

The behaviour of ketones **1** towards compounds **2** is different from that of their homologs like chromanones or tetralones; the formation of pyrano compounds was more difficult and not spontaneous.

Figure 3



	Z	R^2
9a	CN	CH_3
9b	CN	C_2H_5
9c	$COOCH_3$	CH_3

10a

EXPERIMENTAL

Melting points (uncorrected) were determined on a Kofler apparatus. The ir spectra were obtained with a Perkin-Elmer 257 spectrophotometer. The ^1H nmr spectra were recorded in deuteriochloroform as the solvent on a Bruker model AM 300 WB (300 MHz) or a Perkin-Elmer R24B (60 MHz) spectrometer with tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million and signals are quoted as s (singlet), d (doublet), fd (false doublet), t (triplet), q (quartet), m (multiplet). Mass spectra were determined with a Nermag R10-10C mass spectrometer.

2-(2-Cyano-2-methoxycarbonylvinyl)-3-hydroxybenzofuran (**3a**).

Method A.

To a suspension of sodium hydride (0.5 g, 20.8 mmoles) in tetrahydrofuran (20 ml) cooled in an ice bath, 3-oxo-2,3-dihydrobenzofuran **1a** [12] (1.30 g, 9.4 mmoles) in tetrahydrofuran (25 ml) was dropwise added under nitrogen; the mixture was stirred 15 minutes after the end of the addition and methyl 2-cyano-3-methoxypropenoate **2a** (1.55 g, 11 mmoles) in tetrahydrofuran (20 ml) was dropwise added (15 minutes); the mixture was stirred at room temperature 7 hours. Dilute hydrochloric acid 1.2 *M* (100 ml) was added and a gummy precipitate appeared which was dissolved in dichloromethane (200 ml). After drying over magnesium sulfate and evaporation, a yellow solid was obtained; the solid was washed with diethyl ether, yield 0.66 g (28%), mp 244°; ir (potassium bromide): 3120 (OH), 2230 (CN), 1725 and 1660 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): 3.85 (s, 3H, CH_3), 7-7.9 (m, 5H, *H* arom, O*H*), 8.20 (s, 1H, =C*H*); ms: (m/e) 243 (M^+).

Anal. Calcd. for $C_{13}H_9NO_4$: C, 64.20; H, 3.73; N, 5.76. Found: C, 64.52; H, 3.94; N, 5.53.

Method B.

This compound may also be prepared by adding a mixture of compound **1a** and methyl 2-cyano-3-methoxypropenoate **2a** in THF in a suspension of sodium hydride as described for compound **4a**, yield (65%).

Method C.

A mixture of compound **1a** (0.69 g, 5 mmoles), methyl 2-cyano-3-methoxypropenoate (0.75 g, 5.3 mmoles), potassium carbonate (1.38 g, 10 mmoles) in dimethylformamide (20 ml) were stirred 2 days at room temperature. Water (500 ml) was added and the mixture was acidified with hydrochloric acid to *p*H 1; a solid mixture **3a** (*E* + *Z*) precipitated and was filtered, yield 0.80 g (66%).

2-(2-Cyano-2-ethoxycarbonylvinyl)-3-hydroxybenzofuran (**3b**).

Similarly prepared as for compound **3a** from ethyl 2-cyano-3-ethoxypropenoate **2b**, according method C; yield 81%, mp 190°; ir (potassium bromide): 3120 (OH), 2230 (CN), 1725 and 1670 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): 1.45 (t, 3H, CH_3), 4.20 (q, 2H, CH_2), 7-7.7 (m, 5H, *H* arom, O*H*), 8.10 (s, 1H, =C*H*); ms: (m/e) 257 (M^+).

Anal. Calcd. for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44. Found: C, 65.21; H, 4.56; N, 5.69.

2-(2-Cyano-2-methoxycarbonylvinyl)-3-hydroxy-5-chlorobenzofuran (**3c**).

Similarly prepared, as for compound **3a**, from **1c** [12] according to method A and was obtained in a yield of 78%, mp 260°; ir (potassium bromide): 3200 (OH), 2230 (CN), 1720 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): 3.80 (s, 3H, OCH_3), 5.1 (br s, 1H, O*H*), 7.5 (br s, 2H, *H* arom), 7.9 (s, 1H, *H* arom), 8.2 (s, 1H, =C*H*); ms (m/e) 277 (M^+).

Anal. Calcd. for $C_{13}H_8ClNO_4$: C, 56.23; H, 2.90; N, 5.04. Found: C, 56.11; H, 2.98; N, 5.12.

2-(2,2-Diethoxycarbonylvinyl)-3-hydroxybenzofuran (**3d**).

Compound **3d** was similarly obtained from compound **1a**, ethyl 2-ethoxycarbonyl-3-ethoxypropenoate and sodium hydride at room temperature 18 hours; the crude oil after work up was dissolved in diethyl ether from which a solid **3d** slowly (1 month) crystallized, yield (30%), mp 124°; ir (potassium bromide): 3200 (OH), 1725 and 1715 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): 1.4 (m, 6H, CH_3), 4.4 (m, 4H, CH_2), 7-7.9 (m, 5H, *H* arom, O*H*), 8.0 (s, 1H, =C*H*).

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.34; H, 5.25.

2-(2,2-Dimethoxycarbonylethylidene)-3-oxo-2,3-dihydrobenzofuran (**4a**) (*Z* Isomer).

A mixture of compound **1a** (1.38 g, 10 mmoles) and methyl 2-methoxycarbonyl-3-methoxypropenoate (1.84 g, 10.5 mmoles) in tetrahydrofuran (40 ml) was dropwise added (20 minutes) to a suspension of sodium hydride (0.48 g, 20 mmoles) in tetrahydrofuran (20 ml) under nitrogen; the mixture was stirred 1.5 hour at room temperature then at reflux 4 hours; after evaporation, water (100 ml) was added to the residue and then dilute hydrochloric acid was added to *p*H 1; extraction with dichloromethane (2 x 100 ml), drying over magnesium sulfate and evaporation afforded a solid which was chromatographed on a silica gel column (30/75 mesh) using dichloromethane as eluent, yield 1.66 g (60%), mp 124°; ir (potassium bromide): 1745, 1735, 1710 and 1670 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): 3.80 (s, 6H, OCH_3), 4.60 (d, J = 10, 1H, C*H*), 6.33 (d, J = 10, 1H, =C*H*), 7.20 (ft, J = 8.2, 2H, *H*

arom), 7.63 (m, 1H, *H* arom), 7.75 (fd, J = 8.2, 1H, *H* arom); ^{13}C nmr (deuteriochloroform): 49.2 (*C*H), 53.3 (2C) (O*C*H$_3$), 105.4, 113.0, 121.7, 124.7, 124.9, 137.7, 149.8 (*C* arom, =*C*H), 166.3 (*C*OOCH$_3$), 166.8 (*C*OOCH$_3$), 183.4 (*C*=O); ms: (m/e) 276 (M^+).

Anal. Calcd. for $C_{14}H_{12}O_6$: C, 60.87; H, 4.38. Found: C, 60.61; N, 4.59.

2-(2,2-Diethoxycarbonylethylidene)-3-oxo-2,3-dihydrobenzofuran (**4b**) (*Z* Isomer).

Compound **4b** was similarly obtained starting from ethyl 2-ethoxycarbonyl-3-ethoxypropenoate, yield (53%), mp 114°; ir (potassium bromide): 3180 (OH), 1720 and 1660 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): 1.20 (t, J = 8, 6H, C*H*$_3$), 4.1 (q, J = 8, 4H, OC*H*$_2$), 4.73 (d, J = 10, 1H, C*H*(COOCH$_3$)$_2$), 6.36 (d, J = 10, 1H, =C*H*), 7.20 (ft, J = 8, 2H, *H* arom), 7.64 (ft, J = 7.8, 1H, *H* arom), 7.76 (fd, J = 7.8, 1H, *H* arom).

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.04; H, 5.25.

2-Dimethylaminomethylene-3-oxo-2,3-dihydrobenzofuran (**6a**).

3-Oxo-2,3-dihydrobenzofuran (0.69 g, 5 mmoles) was dissolved in absolute ethanol (10 ml); dimethylformamide diethylacetal (0.88 g, 6 mmoles) in ethanol (3 ml) was dropwise added on the refluxing mixture. After 4 hours under reflux, the cooled mixture was evaporated leaving a red solid which was washed with diethyl ether and then chromatographed on a silica gel column (230/400 mesh) using dichloromethane:acetone (60:40, v/v) as eluent, yield 0.65 g (69%), mp 114°; ir (potassium bromide): 1670 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): 3.10 (s, 6H, NC*H*$_3$), 7.1-7.7 (m, 5H, *H* arom, =C*H*).

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 70.07; H, 5.71; N, 7.24.

2-(2-Cyano-2-methoxycarbonylvinyl)-3-hydroxybenzofuran (**3a**).

We used the procedure described by Maitte [6]. Compound **6a** (1.32 g, 7 mmoles) was dissolved in dimethylformamide (8 ml) and methanol (4 ml); ethyl cyanoacetate (0.8 g, 7 mmoles) and benzyltriethylammonium hydroxide, 40% weight solution in methanol, (Triton B) (3.35 ml, 7.3 mmoles) were added to the mixture which was heated 40 minutes at 60°; then ethylcyanoacetate (0.8 g, 7 mmoles) and Triton B (3.35 ml, 7.3 mmoles) were added and the mixture heated 40 minutes at 60°. After cooling, water (30 ml) was added; the mixture was acidified with dilute hydrochloric acid to *p*H 4. An oil was decanted which solidified after one night. The yellow solid was crystallized from methanol, yield 0.425 g (25%), mp 228°.

Using methyl cyanoacetate instead of ethyl cyanoacetate afforded the same compound **3a**, yield (66%).

2-(2-Cyano-2-methoxycarbonylvinyl)-3-hydroxy-5-chlorobenzofuran (**3c**).

Similarly prepared as for compound **3a** starting from compound **6c** was obtained in a yield of 90%.

2-(2,2-Dimethoxycarbonylethylidene)-3-oxo-2,3-dihydrobenzofuran (**4a**).

Similarly prepared from compound **6a** and dimethyl malonate **4a** was obtained in 35% yield.

2-Oxo-3-methoxycarbonyl-2*H*-pyrano[3,2-*b*]benzofuran (**8**).

Method A.

Compound **6a** (0.68 g, 3.6 mmoles) and an excess of dimethyl malonate (8 g, 60 mmoles) were heated 5 hours under reflux. Xylene (20 ml) was added and the mixture was distilled under reduced pressure to a volume of 10 ml; this operation was repeated twice; after cooling a solid crystallized from the mixture; the solid was washed with diethyl ether, yield 0.55 g (62%), mp 193°; ir (potassium bromide): 1765 (br) and 1705 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): 3.95 (s, 3H, OC*H*$_3$), 7.40 (m, 2H, *H* arom), 7.58 (fd, J = 4, 1H, *H* arom), 7.84 (fd, J = 7.9, 1H, *H* arom), 8.62 (s, 1H, = C*H*); ms: (m/e) 244 (M^+).

Anal. Calcd. for $C_{13}H_8O_5$: C, 63.94; H, 3.30. Found: C, 63.61; H, 3.57.

Method B.

Compound **4a** (0.20 g, 0.7 mmole) in xylene (10 ml) was refluxed 24 hours; after cooling a yellow solid **8** precipitated, yield 0.12 g (70%), mp 193°.

2-(2,2-Dimethoxycarbonylethylidene)-3-oxo-2,3-dihydrobenzofuran (**4a**).

Compound **8** (0.4 g, 1.6 mmoles) was dissolved in methanol (15 ml) with a drop of concentrated sulfuric acid and refluxed 24 hours. After evaporation *in vacuo* the residue was treated with water (50 ml), extracted with dichloromethane (2 x 50 ml) and dried over magnesium sulfate. The solid obtained after evaporation was chromatographed on a silica gel column (230/400 mesh) using dichloromethane as eluent, yield 0.21 g (48%); mp 124°.

2-(2,2-Diethoxycarbonylethylidene)-3-oxo-2,3-dihydrobenzofuran (**4b**).

Compound **4a** (0.61 g, 2.2 mmoles), tetraethoxide orthotitanate (0.4 g, 1.75 mmoles) in ethanol (10 ml) were refluxed 4 hours. After evaporation the residue was acidified with dilute hydrochloric acid, extracted with dichloromethane (2 x 50 ml) and dried over magnesium sulfate. After evaporation the residue was chromatographed on a silica gel column (35/70 mesh) with dichloromethane as eluent; yield 0.34 g (51%), mp 114°.

Acylation of Compounds **3** or **4**.

General Procedure.

Compound **3** or **4** (2 mmoles), sodium acetate (2 mmoles), acetic anhydride (10 ml) were heated at 80°. After evaporation to dryness the residue was treated with water (50 ml) and extracted with dichloromethane (2 x 50 ml); the organic extracts were washed with water (2 x 25 ml) and dried over magnesium sulfate. The solid obtained after evaporation was chromatographed on a silica gel column (230/400 mesh) using dichloromethane:petroleum ether 40-60 (50:50, v/v) as the eluent.

2-(2-Cyano-2-methoxycarbonylvinyl)-3-acetoxybenzofuran (**9a**).

This compound was obtained in 68% yield, mp 146°; ir (potassium bromide): 2220 (CN), 1760 and 1710 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): 2.43 (s, 3H, COC*H*$_3$), 3.90 (s, 3H, OC*H*$_3$), 7.1-7.7 (m, 4H, *H* arom), 7.95 (s, 1H, =C*H*).

Anal. Calcd. for $C_{15}H_{11}NO_5$: C, 63.16; H, 3.89; N, 4.91. Found: C, 63.05; H, 4.06; N, 5.08.

2-(2-Cyano-2-ethoxycarbonylvinyl)-3-acetoxybenzofuran (**9b**).

This compound was obtained in 92% yield, mp 135°; ir (potassium bromide): 2220 (CN), 1765 and 1715 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): 1.35 (t, 3H, C*H*$_3$), 2.45 (s, 3H, COC*H*$_3$), 4.35 (q, 2H, C*H*$_2$), 7.1-8.0 (m, 4H, *H* arom), 7.95 (s, 1H, =C*H*).

Anal. Calcd. for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.53; H, 4.31; N, 4.86.

2-(2,2-Dimethoxycarbonylvinyl)-3-acetoxybenzofuran (**9c**).

This compound was obtained in 57% yield, mp 114°; ir (potassium bromide): 1785 and 1715 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): 2.40 (s, 3H, $COCH_3$), 3.84 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.2-7.4 (m, 4H, *H* arom), 7.56 (s, 1H, =C*H*).

Anal. Calcd. for $C_{16}H_{14}O_7$: C, 60.38; H, 4.43. Found: 60.02; H, 4.67.

2-(2,2-Dimethoxycarbonylvinyl)-3-*p*-toluenesulfonyloxybenzofuran (**10a**).

Compound **4a** (0.61 g, 2.2 mmoles) was dissolved in dichloromethane (20 ml) and pyridine (2 ml); *p*-toluenesulfonyl chloride (0.58 g, 3 mmoles) was added and the mixture stirred at room temperature 20 hours. Water (200 ml) was added and the mixture was decanted; the aqueous layer was extracted with dichloromethane (2 x 50 ml). The organic extracts were washed with water (2 x 50 ml) and dried over magnesium sulfate. The solid obtained after evaporation was chromatographed on a silica gel column (230/400 mesh) using dichloromethane:petroleum ether 40-60 (50:50, v/v) as eluent, yield 0.51 g (54%), mp 174°; ir (potassium bromide): 1740, 1730 (CO); ^1H nmr (deuteriochloroform): 2.40 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.90 (s, 1H, =C*H*), 7.10-7.44 (m, 6H, *H* arom), 7.52 (fd, J = 8.5, 1H, *H* arom), 7.77 (fd, J = 8.5, 1H, *H* arom).

Anal. Calcd. for $C_{21}H_{18}O_8S$: C, 58.60; H, 4.22. Found: C, 58.94; H, 4.15.

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