FURAN RING OPENING REACTIONS OF 5-HYDROXY-2,3-DIHYDROBENZO[*b*]FURANS

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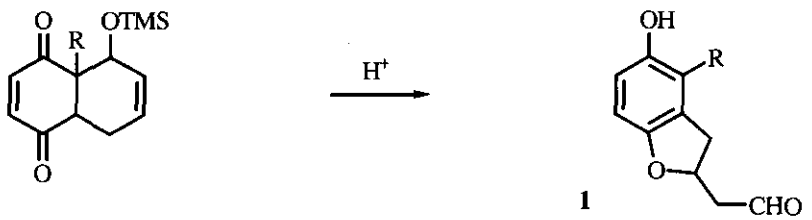
Abstract - A furan ring opening of benzo[*b*]furans (**1a-c**) under acetylation and methylation conditions was carried out. The reaction of these heterocycles with acetic anhydride-pyridine mixture afforded the corresponding 1,4-disubstituted buta-1,3-dienes (**3a-c**). Compound (**3c**) reacts with dimethyl sulfate under basic conditions to give 1-methoxy-4-(3,6-dimethoxy-2-nitrophenyl)-buta-1,3-diene (**5**) in 95 % yield. Some evidences on the participation of carbanion intermediates and a possible reaction course for the furan ring opening of heterocycles (**1a-c**) are presented.

In previous works on the chemistry of activated quinones we have described the preparation of 5-hydroxy-2,3-dihydrobenzo[*b*]furans and their application to the synthesis of carbocyclic quinones.[1-7] Recently we have reported two new access to highly functionalized 5-hydroxy-2,3-dihydro-benzo[*b*]furans of type (**1**) and (**2**) which are based on: a) acid-induced rearrangement of Diels-Alder adducts of activated benzoquinones with (*E*)-1-trimethylsiloxybuta-1,3-diene[8-10] and b) reaction of activated benzoquinones with methacrolein N,N-dimethylhydrazone.[11]

Our interest to develop new methods for the synthesis of carbo- and heterocyclic quinones led us to investigate the heterocyclic ring opening of benzofurans in order to obtain aromatic precursors of heterobicyclic quinones. Now we wish to report the results of our work on the furan ring opening of heterocycles of type (**1**).



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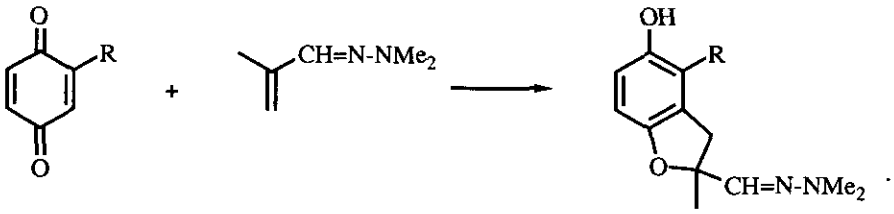

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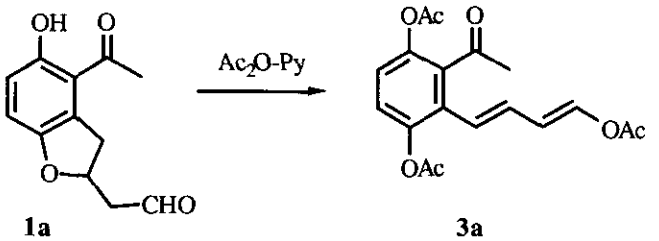
Taking into accounts previous results on the heterocyclic ring opening of related benzofurans with acylating agents,[2,5] we attempted to induce the cleavage of the furan ring on compound (**1a**) by reaction with acetic anhydride in the presence of pyridine. The progress of the reaction was monitored by thin layer chromatography and the complete disappearance of starting material (**1a**) was observed after two days. The gradual disappearance of **1a** was accompanied by the appearance of a single distinct compound which was isolated and characterized as diene (**3a**). The structure of **3a** was mainly established by its ^{1}H-nmr spectrum and decoupling experiments. The ^{1}H-nmr spectrum of **3a** showed three OCOMe singlets (δ 2.20, 2.28, and 2.32 ppm), a COMe singlet (δ 2.40 ppm), an AB aromatic system (δ 7.04 and 7.14 ppm; J= 8 Hz) and four CH= protons (δ 6.13; J=12, 8 and 2 Hz; δ 6.34; J= 14 Hz; δ 6.38; J= 14 and 8 Hz; δ 7.48; J= 12 Hz).



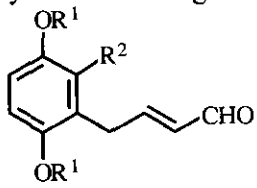
1a **3a**

The participation of the pyridine in the rearrangement of compound (**1a**) was confirmed through an experiment in which the substrate (**1a**) was left in acetic anhydride solution for 5 days at room temperature and recovered.

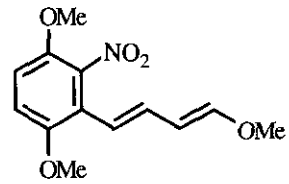
In view of the facile furan ring opening of compound (**1a**), we wanted to explore the scope of this reaction with benzofurans (**1b,c** and **1c**). These compounds, prepared as previously

reported,[9] were subjected to reaction with acetic anhydride-pyridine mixture at room temperature. However, under these conditions a partial conversion of the benzofurans to the corresponding 1,3-dienes was observed and, interestingly, in an experiment with furan (**5**) the signals of arylcrotonaldehyde (**4a**) were detected by ^{1}H-nmr in the crude product. When the reaction mixtures were heated to 50-55 °C the transformation of furans (**1b-c**) was completed after two days and the corresponding dienes (**3b-c**) were isolated (Table 1).

We also explored the furan ring opening of heterocycle (**1c**) under methylation conditions. Thus, the reaction of heterocycle (**1c**) with excess dimethyl sulfate, potassium carbonate in benzene solution at reflux gave 1,3-diene (**5**) in 95% yield. This compound is unstable and undergoes hydrolysis on standing to afford arylcrotonaldehyde (**4b**).

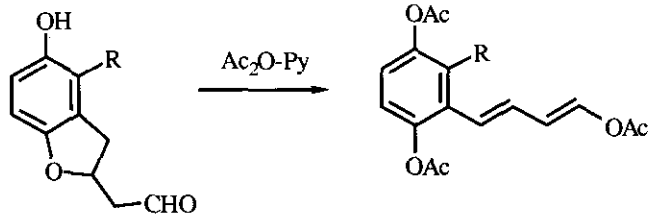


4a: R^1=Ac, R^2=CO_2Me
4b: R^1=Me, R^2=NO_2



5

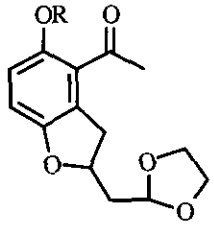
Table1. 1-Acetoxy-4-arylbuta-1,3-dienes (**3a-c**) generated from 2-oxoethylbenzo[*b*]furans (**1a-c**) with acetic anhydride-pyridine.



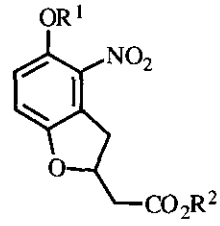
1a-c **3a-c**

Benzofuran	R	1,3-Diene	Yield(%)
1a	COMe	**3a**	64
1b	CO_2Me	**3b**	50
1c	NO_2	**3c**	80

The furan ring opening of heterocycles of type (**1**) probably involves the participation of a carbanion generated by reaction of the base with an α-hydrogen atom to the aldehyde group. In order to support this assumption we investigated the reactivity of ethylene acetal (**6a**). This compound, prepared in 75% yield from furan (**1a**), was reacted with acetic anhydride-pyridine mixture to afford acetate (**6b**) in 72 % yield. The reluctance of the acetals (**6a,b**) to undergo furan ring opening under the aforementioned conditions is in agreement with the participation of a base-induced retro-Michael carbon-oxygen bond cleavage in the furan ring opening of benzofurans (**1a-c**).



6a: R=H
6b: R=Ac



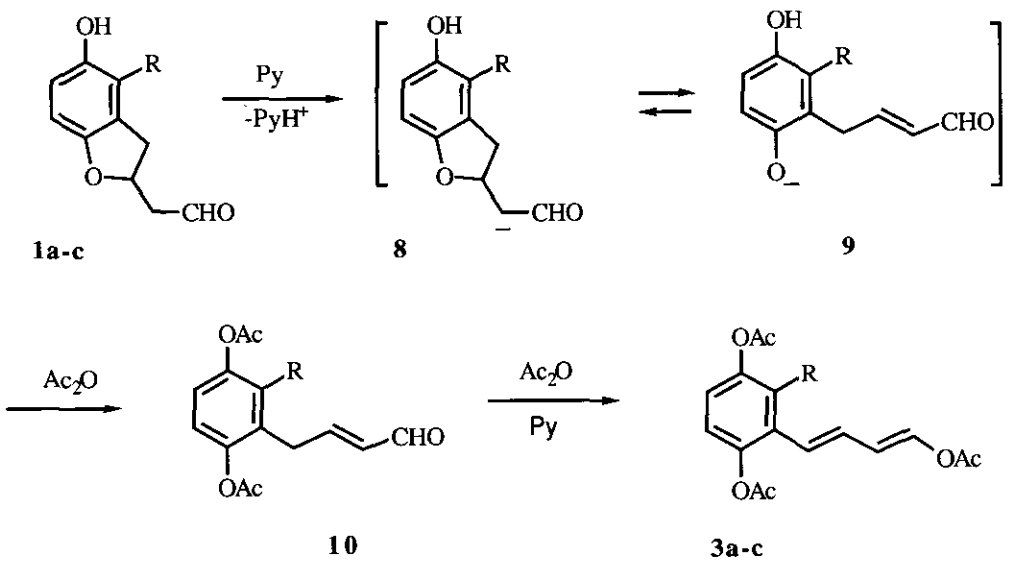
7a: R^1=R^2=H
7b: R^1=R^2=Me

With the aim to know the scope of the above rearrangement we also examined the behaviour of benzofuran (**7a**). This compound which was synthesized in 77% yield by oxidation of benzofuran (**1c**) with sodium hypochlorite[12] was reacted with dimethyl sulfate under the above mentioned conditions to afford compound (**7b**) in 94% yield.

Attempts to induce the ring opening of compound (**7b**) by treatment with hot acetic anhydride-pyridine solution was also unsuccessful and substrate (**7b**) was recovered.

These results indicate that the heterocyclic ring opening in benzofurans (**1a-c**) under the employed methylation and acetylation conditions depends on the acidity of the α-protons to the aldehyde group .

All these results suggest that the furan ring opening of benzofurans (**1a-c**) proceeds through an 5-*exo-trigonal* reverse process giving the corresponding 1,3-dienes (**3a-c**) as oulined in Scheme 1 for the reaction of **1a-c** with acetic anhydride-pyridine mixture.



Scheme 1

These rearrangements are probably initiated by formation of carbanion intermediates (**8**) which by a carbon-oxygen bond cleavage led to phenoxide ion (**9**). Subsequent reaction of **9** with acetic anhydride affords intermediates (**10**) which by dienol-acetylation gave the corresponding 1,4-disubstituted buta-1,3-diene (**3a-c**). The participation of compounds type (**10**) in these rearrangements is supported by the fact that the compound (**4a**) was detected by ^{1}H-nmr during the treatment of compound (**1b**) with an acetic anhydride-pyridine mixture.

According to the mechanism proposed for this furan ring opening, the electron-withdrawing groups at the 4-position in the substrates (**1a-c**) probably favors the carbon-oxygen bond rupture by stabilization of the phenoxide ion (**9**). However, this assumption must be confirmed in the light of experiments with type **1** heterocycles containing electron-donating groups at the 4-position.

In conclusion this study demonstrates that benzofurans of type (**1**) react with acetic anhydride or dimethyl sulfate, under basic conditions, to afford highly functionalized 1,2,3,4-tetrasubstituted arenes which are of potential interest in the synthesis of heterobicyclic quinones.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer model 1310 spectrophotometer for KBr disc and the wave numbers are given in cm^{-1}. ^{1}H-Nmr spectra were taken on a Varian XL-100 and Bruker AC-200 spectrometer in $CDCl_3$ solution. ^{13}C-Nmr spectra were recorded on a Varian XL-300 spectrometer in $CDCl_3$ solution. Chemical shifts are reported in ppm (δ) downfield from Me_4Si. The mass spectra were determined on a VG-12-250 spectrometer at the Instituto de Química Orgánica General (C. S. I. C.), Madrid, Spain. Silica gel Merck 60 (70-230 mesh) and DC-Alufolien $60F_{234}$, were used for preparative column chromatography and analytical tlc, respectively.

Reaction of furan (1a) with acetic anhydride-pyridine mixture. A solution of furan (**1a**) (490 mg, 2.08 mmol), acetic anhydride (6 ml, 63.59 mmol) and dry pyridine (0.6 ml, 7.42 mmol) was allowed to react at room temperature for two days. The mixture was poured into an ice-water solution and the precipitate was filtered to afford crude 1-acetoxy-4-(2-acetyl-3,6-diacetoxyphenyl)-buta-1,3-diene (**3a**) (464 mg, 64%); mp 120-122°C (from ethanol); Anal. Calcd for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found: C, 62.16; H, 5.82; ν_{max} cm^{-1}: 1760 (OC=O), 1700 (C=O), 1640 (C=C), 1180(O-CO), 1100 (H-C=C-H); δ_H (300 MHz): 2.17 (s, 3H, 1-OAc), 2.25 (s, 3H, OAc), 2.30 (s, 3H, OAc), 2.38 (s, 3H, COMe), 6.13 (ddd, 1H, $J_{2,1}$=12; $J_{2,3}$=8; $J_{2,4}$=2 Hz, 2-H), 6.34 (d, 1H, $J_{4,3}$=14 Hz, 4-H), 6.38 (dd, 1H, $J_{3,4}$=14; $J_{3,2}$=4 Hz, 3-H), 7.04 (d, 1H, $J_{5',4'}$=8 Hz, 4'-H), 7.14 (d, 1H, $J_{4',5'}$= 8 Hz, 5'-H), and 7.48 (d, 1H, $J_{1,2}$=12 Hz, 1-H).

Reaction of furan (1b) with acetic anhydride-pyridine mixture. A solution of (**1b**) (197 mg, 0.84 mmol), acetic anhydride (4 ml, 42.39 mmol) and dry pyridine (0.4 ml, 4.94 mmol) was heated to 50-55°C for two days. The reaction mixture was cooled to room temperature and poured into an ice-water solution to give 1-acetoxy-4-(3,6-diacetoxy-2-methoxycarbonylphenyl)-buta-1,3-diene (**3b**) as pale yellow solid; mp 120-122°C (from ethanol); Anal. Calcd for $C_{18}H_{18}O_8$: C, 59.66; H, 5.01. Found: C, 59.49; H, 4.40; ν_{max} cm^{-1}: 1750 (OC=O), 1200 (C-O), 1100 (H-C=C-H); δ_H (300 MHz): 2.16 (s, 3H, 1-OAc), 2.20 (s,

3H, OAc), 2.28 (s, 3H, OAc), 3.87 (s, 3H, CO_2Me), 6.15 (dd, 1H, $J_{2,1}$=12; $J_{2,3'}$=10 Hz, 2-H), 6.40 (d, 1H, $J_{4,3}$=14 Hz, 4-H), 6.45 (dd, 1H, $J_{3,4}$=14; $J_{3,2}$=10 Hz, 3-H), 7.05 (d, 1H, $J_{5,4}$=8 Hz, 4-H), 7.20 (d, 1H, $J_{4,5}$= 8 Hz, 5-H), and 7.40 (d, 1H, $J_{1,2}$=12 Hz, 1-H).

Reaction of benzofuran (1c) with acetic anhydride-pyridine mixture. Following the same procedure previously described for the reaction of furan (**1b**), treatment of the heterocycle (**1c**) (170 mg, 0,76 mmol) with acetic anhydride (3 ml, 31.79 mmol) and dry pyridine (0.3 ml, 3.70 mmol) afforded 1-acetoxy-4-(3,6-diacetoxy-2-nitrophenyl)-buta-1,3-diene (**3c**) (210 mg, 80%) as solid; mp 126-128 °C (from ethanol); Anal. Calcd for $C_{16}H_{15}O_8N$: C, 55,01; H, 4,29; N, 4,01. Found: C, 54,89; H, 4,52; N, 3,70; ν_{max} cm^{-1}: 1770-1740 (C=O), 1630 (C=C), 1520 and 1350 (NO_2); δ_H (100 MHz): 2,08 (s, 3H, 1-OAc), 2,34 (s, 6H, 2x OAc), 6.16 (dd, 1H, $J_{2,1}$=12; $J_{2,3}$=12 Hz, 2-H), 6.48 (d, 1H, $J_{4,3}$=14 Hz, 4-H), 6.70 (dd, 1H, $J_{3,4}$=14; $J_{3,2}$=12 Hz, 3-H), 7.27(s, 2H, 4-H and 5-H), 7.58(d, 1H, $J_{1,2}$=12 Hz, 1-H).

Reaction of (1c) with dimethyl sulfate A solution of the heterocycle (**1c**) (385 mg, 1,72 mmol), dimethyl sulfate (532 mg, 4.30 mmol) and potassium carbonate (500 mg, 5.05 mmol) in benzene (30) was refluxed for 4 h. The solution was filtered, the solvent was removed under reduced pressure, and the residue was dissolved in 5% methanolic potassium hydroxide (30 ml) and the solution was left overnight at room temperature. The mixture was extracted with chloroform (2x30 ml), and the extract was washed with water and dried over magnesium sulfate. Removal of the solvent under reduced pressure gave crude 1-methoxy-4-(3,6-dimethoxy-2-nitrophenyl)-buta-1,3-diene (**5**) (435 mg, 95%) as an oil; ν_{max} cm^{-1}: 1600 (C=C), 1520 (NO_2), 1360 (NO_2); δ_H (100 MHz): 3,66 (s, 3H, OMe), 3,86 (s, 3H, OMe), 3,88 (s, 3H, OMe), 5,68 (dd, 1H, $J_{2,1}$=14; $J_{2,3}$= 10 Hz, 2-H), 6,16 (d, 1H, $J_{4,3}$= 16 Hz, 4-H), 6,7-7,1 (m, 4H, 2-H, 1-H, 4'-H, and 5'-H).

Attempts to prepare an analytical sample of **5** by column chromatography on silica gel (benzene) were unsuccessful due to the extensive hydrolysis to compound (**4b**). From this mixture, a pure sample of 4-(2,6-dimethoxy-2-nitrophenyl)-but-2-enal (**4b**) (liquid) was

obtained by column chromatography on silica gel (chloroform); Anal. Calcd for $C_{12}H_{13}O_5N$: C, 57.37; H, 5,18; N, 5.58. Found: C, 57.50; H, 5.26; N, 5.80; ν_{max} cm^{-1}: 1670 (C=O), 1520, 1360 (NO_2); δ_H (100 MHz): 3.55 (br d, 2H, J =7 Hz, 4-H), 3.88 (s, 3H, OMe), 3.90 (s, 3H, OMe), 6.04 (dd, 1H, $J_{2,3}$=14; $J_{2,1}$=8 Hz, 2-H), 6.80-7.20 (m, 3H, 3-H, 4'-H and 5'-H), 9.62 (d, 1H, $J_{1,2}$= 8 Hz, CHO); ms m /z (%): 251 (M^+, 10), 237 (35), 191 (94), 77 (100).

4-Acetyl-5-hydroxy-2-(2,2-ethylendioxyethyl)-2,3-dihydrobenzo[b]furan (6a). A solution of furan (**1a**) (225 mg, 1.022 mmol), ethylene glycol (0.6 ml, 10.8 mmol) and *p*-toluensulphonic acid (50 mg) in benzene (50 ml) was refluxed for 2 h. The mixture was washed with water, dried ($MgSO_4$) and evaporated. Removal of the solvent afforded the acetal (**6a**) as yellow solid (204 mg, 75%); mp 96-98°C (from ethanol); Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10. Found: C, 63.13; H, 6.05. ν_{max} cm^{-1}: 1630 (C=O), 1220 (O-C); δ_H (100 MHz): 1.86-2.45 (m, 2H, 1'-H), 2.56 (s, 3H, COMe), 3.21 (dd, 1H, $J_{3,3}$=16; $J_{3,2}$=8 Hz, 3-H), 3.61 (dd, 1H, $J_{3,3}$=16; $J_{3,2}$= 9 Hz, 3-H'), 3.82-4.80 (m, 4H, OCH_2CH_2O), 4.80-5.11(m, 1H, 2-H), 5.08(dd, 1H, $J_{2',1}$=6; $J_{2',1'}$=4 Hz, 2'-H), 6.76 (d, 1H, $J_{6,7}$=9 Hz, 6-H), 6.94 (d, 1H, $J_{7,6}$=9 Hz, 7-H), and 12.16 (s, 1H, OH).

Reaction of acetal (6a) with acetic anhydride-pyridine mixture. A solution of acetal (**12**) (85 mg, 0.32 mmol), acetic anhydride (2 ml, 21.19 mmol) and pyridine (0.2 ml, 2.47 mmol) was left at room temperature for 2 days. The mixture was poured into an ice-water solution and the solid was filtered to afford 5-acetoxy-4-acetyl-2-(2,2-ethylendioxyethyl)-2,3-dihydro-benzo[*b*]furan (**6b**) (71 mg, 72 %) as white solid; mp 96-97 °C (from ethanol); Anal. Calcd for: $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.47; H, 6.03; ν_{max} cm^{-1} 1740 (OCOMe), 1700 (COMe), 1200 (O-CO); δ_H (200 MHz): 1.94-2.10 (m, 1H, 1'-H), 2.18-2.34 (m, 1H, 1'-H'), 2.31 (s, 3H, OCOMe), 2.49 (s, 3H, COMe), 3.13 (dd, 1H, $J_{3,3}$=17; $J_{3,2}$= 8 Hz, 3-H), 3.52 (dd, 1H, $J_{3,3}$=17; $J_{3,2}$=9 Hz, 3-H'), 3.84-4.07 (m, 4H, OCH_2-CH_2O), 4.94-5.10 (m, 1H, 2-H), 5.08 (dd, 1H, $J_{2',1'}$=6; $J_{2',1'}$ =3.8 Hz, 2'-H), 6.86 (s, 2H, 6-H and 7-H).

2-(5-hydroxy-4-nitro-2,3-dihydrobenzo[b]furan-2-yl) acetic acid (7a). A solution of sodium hypochlorite (50 mg, 0.55 mmol) and aminosulfonic acid (50 mg, 0.51 mmol) in water (2 ml) was added to a stirred solution of **4a** (100 mg, 0,44 mmoles) in acetone-water (7 ml, 3:1) and the mixture was left, with stirring, for 40 min at room temperature. The solution was poured into saturated aqueous sodium bicarbonate (5 ml) and extracted with ether (2x10 ml). The aqueous solution was acidified with 5% hydrochloric acid and then extracted with ether (2x 15 ml). The organic extract was washed with water and dried over magnesium sulfate. Removal of the solvent afforded crude acid (**7a**) (82 mg, 77%) which was purified by column chromatography on silica gel (chloroform-ethyl acetate; 1:1); mp 185-186.5°C (from ethanol-benzene; 1:1). Anal. Calcd for: $C_{10}H_9NO_6$: C, 50.20; H, 3.77; N, 5.86. Found: C, 50.01; H, 4.00; N, 5.70; ν_{max} cm^{-1}: 3600-3000 (O-H), 1700 (C=O), 1520 (NO_2); δ_H (100 MHz): 2.75 (m, 2H, 2-H), 3.32 (dd, 1H, $J_{3',3'}$=20; $J_{3',2'}$=8 Hz, 3'-H), 3.76 (dd, 1H, $J_{3',3'}$=20; $J_{3',2'}$=9 Hz, 3'-H'), 5.15 (m, 1H, 2'-H), 6.40 (br s, 1H, OH), 6.85 (d, 1H, $J_{6',7'}$= 9 Hz, 6'-H), 7.00 (d, 1H, $J_{7',6'}$= 9 Hz, 7'-H), 9.80 (s, 1H, OH).

Reaction of furan (7a) with dimethyl sulfate. A stirring solution of acid (**7a**) (268 mg, 1.0 mmol), dimethyl sulfate (666 mg, 5.29 mmol) and potassium carbonate (2.0 g, 14.50 mmol) in benzene-acetone (50 ml, 1:2) was heated at reflux for 3 h. The mixture was filtered and the filtrate was poured into methanol-water (30 ml, 1:1) and the solution was left overnight at room temperature for 2 days. The resulting alkaline mixture was extracted with chloroform (2x30 ml) and the extract was washed with water and dried over magnesium sulfate. Removal of the solvent under reduced pressure afforded 5-methoxy-2-(methoxycarbonylethyl)-4-nitro-2,3-dihydro-benzo[*b*]furan (**7b**) as orange solid; (283 mg, 94%); mp 69-71°C (from benzene-petroleum ether 40-60°); Anal. Calcd for $C_{12}H_{13}O_6N$: C, 53,93; H, 4,86; N, 5,24. Found: C, 53,62; H, 5,03; N, 4,89; ν_{max} cm^{-1}: 1720 (C=O),1520 (NO_2), 1360 (NO_2); δ_H (100 MHz): 2.71 (dd, 1H, $J_{1',1'}$=18, $J_{1',2}$=9 Hz, 1'-H), 2.87 (dd, 1H, $J_{1',1'}$=18; $J_{1',2}$=8 Hz, 1'-H'), 3.17 (dd, 1H, $J_{3,3}$=20; $J_{3,2}$=9 Hz, 3-H), 3.64 (dd, 1H, $J_{3,3}$=20; $J_{3,2}$=9 Hz, 3-H'), 3.74 (s, 3H, OMe), 3.87 (s, 3H, OMe), 5.25 (m, 1H, 2-H)), 6.86 (d, 1H, $J_{6,7}$= 8 Hz, 6-H), 6,88 (d, 1H, $J_{7,6}$=8 Hz, 7-H); δ_C (50 MHz): 35.41, 40.25, 51.95,

57.47, 79.77, 113.39, 113.76, 123.11, 147.02, 153.45, 170.30; ms m/z (%): 267(M^+, 25), 250 (100), 232 (14), 194 (59).

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