STUDIES ON QUINONES. PART 26.[1] THE REACTION OF METHACROLEIN *N,N*-DIMETHYLHYDRAZONE WITH ACTIVATED BENZOQUINONES

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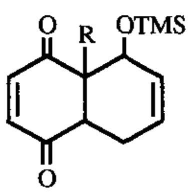
Abstract -A one-step formation of 5-hydroxy-2,3-dihydrobenzo[*b*]furans by a [3+2] addition process of methacrolein *N,N*-dimethylhydrazone (**4**) with a variety of 1,4-benzoquinones bearing activating groups is reported.

We have recently described[2,3] that adducts of type (**1**), prepared by Diels-Alder reaction of activated 1,4-benzoquinones with the (*E*)-1-trimethylsiloxybuta-1,3-diene,[4] undergo selective cleavage of one of the two carbon-carbon bonds generated in the cycloaddition to afford 5-hydroxy-2,3-dihydrobenzo[*b*]furan derivatives (**2**). Our interest to extend these selective cleavage in synthesis of new functionalized 5-hydroxy-2,3-dihydrobenzo[*b*]furans lead us to investigate the possibility to induce carbon-nitrogen fission in the Diels-Alder adducts (**3**) wich could arise from the cycloaddition of methacrolein *N,N*-dimethylhydrazone (**4**) with activated quinones (**6**). The azadiene (**4**) and related azadienes have been successfully used for several authors to prepare azaanthraquinones through cycloaddition reactions.[5-10]



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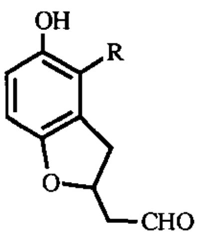

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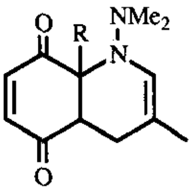

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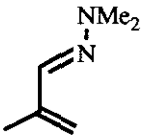

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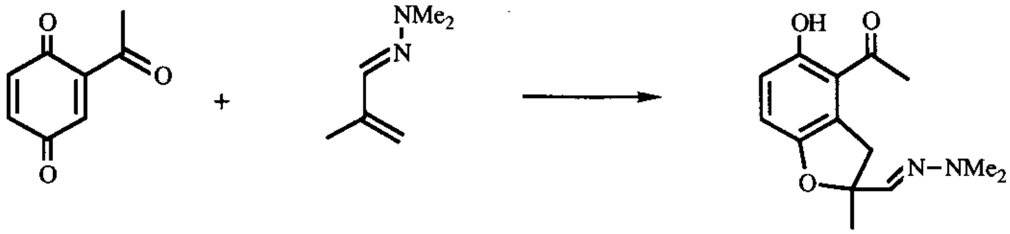
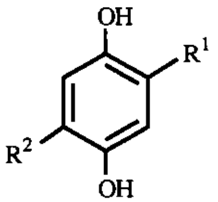
The reaction of azadiene (**4**) with activated quinones was first studied with quinone (**6a**) in dichloromethane solution at room temperature. The reaction proceeds fast to afford a substance which exhibited infrared absorptions at ν 3200 and 1630 cm^{-1}. The ^1H-nmr spectrum reveals three singlet signals of methyl groups at δ1.65, 2.66 and 2.83 ppm, two AB systems at δ 3.26 / 4.08 (J = 16 Hz) and δ 6.79 / 6.97 ppm (J =9 Hz), and two singlet signals at δ 6.70 and 12.18 ppm. These spectral properties along with the ^{13}C-nmr spectrum are in accord with compound (**7a**), which was apparently formed by nucleophilic attack of hydrazone (**4**) at the activated C-3 position of quinone (**6a**).

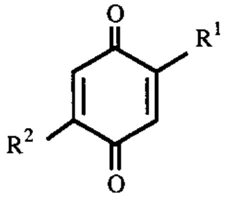


6a **4** **7a**

In view of this interesting formation of the 2,3-dihydrobenzo[*b*]furan system under mild conditions, we wanted to know the scope of the reaction of hydrazone (**4**) with the activated quinones (**6b-f**).



5a-c

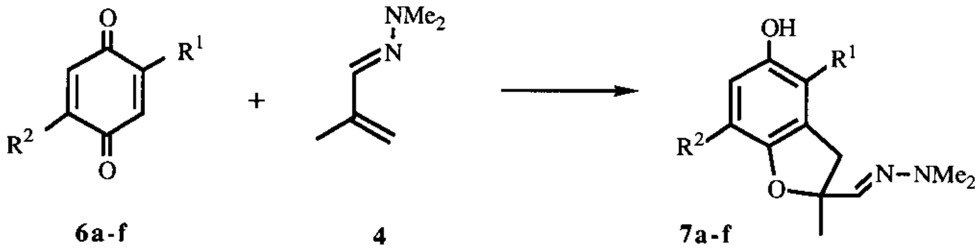


6a-f

	R^1	R^2
6a	COMe	H
6b	CO_2Me	H
6c	COCH=CHPh	H
5a, 6d	CHO	H
5b, 6e	NO_2	H
5c, 6f	NO_2	Br

Compounds (**5b,c**) required to prepare quinones (**6e,f**) were synthesized in 84 and 89% yields by demethylation of the corresponding dimethyl ethers with hydrobromic acid. The reactions of quinones (**6b,c**) were carried out by treatment with hydrazone (**4**) and, in the case of the unstable quinones (**6d-f**), these were generated by oxidation of the corresponding hydroquinones (**5a-c**) with silver (II) oxide, in the presence of **4**. In all the experiments a sole product, characterized as the corresponding benzo[*b*]furan (**7**), was detected by tlc. The results, summarized in Table 1, indicate that hydrazone (**4**) reacts exclusively as a nucleophile adding to the 3-position of quinones (**6a-f**) to provide 2,3-dihydrobenzo[*b*]furans through a [3+2] process. The behavior of compound (**4**) acting as a nucleophile instead of a diene with compounds (**6**) may be due to the highly electrophilic character of these activated quinones.

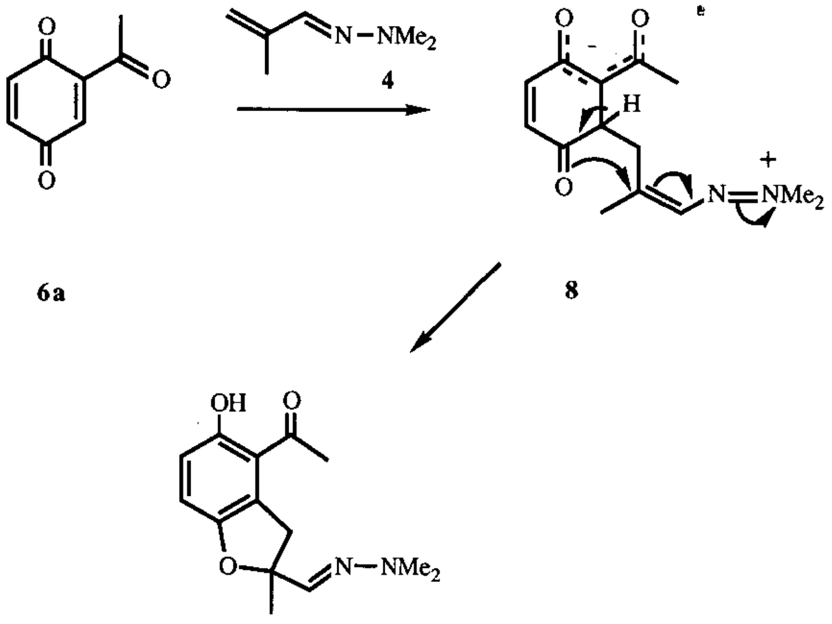
Table 1. Benzo[*b*]furans (**7a-f**) generated by reaction of activated quinones (**6a-f**) with hydrazone (**4**).



Quinone	R^1	R^2	Benzo[*b*]furan	Yield(%)
6a	COMe	H	**7a**	66
6b	CO_2Me	H	**7b**	54
6c	COCH=CHPh	H	**7c**	100
6d	CHO	H	**7d**	97
6e	NO_2	H	**7e**	82
6f	NO_2	Br	**7f**	40

It is noteworthy that Echavarren[11] has reported that the proper 1,4-benzoquinone is unreactive to the Diels-Alder reaction with some α,β-unsaturated *N,N*-dimethylhydrazones, however, when the reaction was carried out in the presence of boron trifluoride etherate the formation of 5-hydroxybenzo[*b*]furans was induced. More recently, Fillion[12] has described the reaction of quinoline-5,8-quinones with 2-ethoxy-2-butenal *N,N*-dimethylhydrazone afforded furoquinolines as the main products along with [4+2] cycloadducts.

The benzo[*b*]furan formation described in this paper is similar to the reaction of activated benzoquinones with enamines which afforded 2,3-dihydrobenzo[*b*]furan derivatives.[13] On the basis of this analogy, the formation of compounds (**7**) probably occurs in a two step sequence as shown for **7a** in which, hydrazone (**4**) acts as a Michael donor with the highly electrophilic quinone (**6a**) to give stabilized intermediate (**8**) which by a subsequent 5-exo-trig cyclization afforded heterocycle (**7a**).



6a

8

7a

In conclusion, the results in the present study indicate that the formation of [3+2] cycloadducts is general in the reaction between activated benzoquinones with methacrolein *N,N*-dimethylhydrazone (**4**). Further studies on the behaviour of other α,β-unsaturated *N,N*-dimethylhydrazones with activated quinones is under investigation.

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 determined on a Varian XL-100 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 spectrum was determined on a VG-12-250 spectrometer. Silica gel Merck HF_{254} (typ 60) and DC-Alufolien $60F_{234}$, were normally used for preparative and analytical tlc, respectively.

REACTIONS OF QUINONES (6a-c) WITH HYDRAZONE (4).

4-Acetyl-5-hydroxy-2-methyl-2,3-dihydrobenzo[*b*]furan-2-carboxaldehyde-*N*,*N*-dimethylhydrazone (7a). To a stirred solution of **6a**[14] (86 mg, 0.57 mmol) in dichloromethane (10 ml), a solution of hydrazone (**4**)[15] (70 mg, 0.63 mmol) in dichloromethane (5 ml) was added dropwise at ambient temperature. The mixture was left for 2 h and the solvent was removed under reduced pressure to afford **7a** (100 mg, 66%) as pale yellow solid mp 76-77°C (petroleum ether; 40-60°C); ir: 3200 (O-H), 1630 (C=O); ^{1}H-nmr : δ 1.65 (s, 3H, 2-Me), 2.66 (s, 3H, COMe), 2.83 (s, 6H, NMe_2), 3.26 (d, 1H, $J_{3,3'}$=16, 3-H), 4.08 (d, 1H, $J_{3',3}$=16, 3'-H), 6.70 (s, 1H, CH=N), 6.79 (d, 1H, $J_{6,7}$=9, 6-H), 6.79 (d, 1H, $J_{7,6}$=9, 7-H), 12.18 (s, 1H, OH); ^{13}C-nmr: δ 26.00, 31.31, 42.59, 43.28, 87.69, 117.59, 117.64, 118.06, 126.25, 135.40, 151.15, 157.31, 204.04. Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.41; H, 7.08; N, 10.44.

5-Hydroxy-4-methoxycarbonyl-2-methyl-2,3-dihydrobenzo[*b*]furan-2-carboxaldehyde *N*,*N*-dimethylhydrazone (7b). According to the above procedure the reaction of quinone (**6b**)[14] (98 mg, 0.59 mmol) with hydrazone (**4**)(66 mg, 0.59 mmol) for 45 min afforded crude heterocycle (**7b**). Preparative tlc using chloroform as the eluent gave pure **7b** (88 mg, 54 %); mp 93-94°C; ir: 3200 (O-H), 1670 (C=O); ^{1}H-nmr: δ 1.60 (s, 3H, 2-Me), 2.82 (s, 6H, NMe_2), 3.28 (d, 1H, $J_{3,3'}$ =18, 3-H), 3.88 (d, 1H, $J_{3',3}$ =18, 3'-H), 3.99 (s, 3H, CO_2Me), 6.72 (s, 1H, CH=N), 6.79 (d, 1H, $J_{6,7}$= 9, 6-H), 6.93 (d, 1H, $J_{7,6}$ =9, 7-H), 10.40 (s, 1H, OH). Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.23; H, 6.69; N, 9.55.

4-Cinnamoyl-5-hydroxy-2-methyl-2,3-dihydrobenzo[*b*]furan-2-carboxaldehyde *N,N*-dimethylhydrazone (7c). A solution of 2,5-dihydroxychalcone (200 mg, 0.83 mmol) in benzene-dichloromethane (1:1; 10 ml), manganese dioxide[14] (0.7 g, 8.04 mmol)) and magnesium sulfate (0.5 g, 4.15 mmol) was vigorously stirred for 30 min at room temperature. The mixture was filtered , the solids were washed with dichloromethane and the solvents were removed under reduced pressure to afford quinone **7c** (197 mg, 100 %) as an orange solid, mp 110-112°C (cyclohexene) (lit.,[16] mp 110-114 °C).

According to the procedure to convert **6a,b** into furans (**7a,b**) the reaction of quinone (**6c**) (81 mg, 0.34 mmol) with hydrazone (**4**) (42 mg, 0.37 mmol) for 2.5 h afforded heterocycle (**7c**). Preparative tlc using chloroform as the eluent gave pure **7c** (114 mg, 96 %); mp 131-133 °C; ir: 3400 (O-H), 1630 (C=O); ^{1}H-nmr: δ 1.66 (s, 3H, 2-Me), 2.86 (s, 6H, NMe$_2$), 3.30 (d, 1H, $J_{3,3'}$=16, 3-H), 4.11 (d, 1H, $J_{3',3}$=16, 3'-H), 6.70 (s, 1H, CH=N), 6.86 (d, 1H, J =16, CO-CH=CH), 6.90-7.80 (m, 7H, arom.), 7.90 (d, 1H, J =16, CO-CH=CH), 12.15 (br s, 1H, OH); ^{13}C-nmr: δ 25.71, 42.67, 43.28, 88.04, 117.71, 118.09, 118.59, 124.44, 125.44, 128.63, 129.10, 130.86, 134.72, 135.40, 144.80, 151.41, 157.83, 194.38. Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 8.00. Found: C, 71.85; H, 6.40; N, 7.82.

1,4-Dihydroxy-2-nitrobenzene (5b). A solution of 1,4-dimethoxy-2-nitrobenzene (5 g, 27.3 mmol), hydrobromic acid (48%, 50 ml), and acetic acid (20 ml) was heated to 110 °C for 28 h. The hot mixture was diluted with water (200 ml) and neutralized with solid sodium bicarbonate. The resulting solution was extracted with chloroform (300 ml) for 17 h in a liquid-liquid continous extraction apparatus. Removal of the solvent afforded crude compound (**5b**) which was chromatographied on silica gel (chloroform) to afford pure **5b** (3.55 g, 84 %) as an orange solid; mp 132-133 °C (lit.,[17] mp 133-134 °C).

2-Bromo-1,4-dihydroxy-5-nitrobenzene (5c). A solution of 2-bromo-1,4-dimethoxy-5-nitrobenzene (0.5 g, 2.3 mmol), hydrobromic acid (48%, 16 ml), and acetic acid (5.7 ml) was heated to 100-110 °C for 3 days. The mixture was diluted with water (100 ml), neutralized with solid sodium bicarbonate and extracted with chloroform (2 x 50 ml). The extract was dried over magnesium sulfate and evaporated off to afford crude **5c**. Column chromathography on silica gel (chloroform) yield pure **5c** (400 mg, 89 %); mp 110-111°C; ir: 3430 (O-H), 1520, 1300 (NO$_2$); ^{1}H-nmr (acetone-d$_6$): δ 7.46 (s, 1H, 3-H), 7.69 (s, 1H, 6-H), 9.53 br s, 1H, OH); ms m/z (%): 239.4 (M$^+$ + 2, 53), 232.9 (M$^+$, 70). Anal. Calcd for $C_6H_4NO_4Br$: C, 30.79; H, 1.72; N, 5.99. Found: C, 30.55; H, 1.47; N, 6.12.

4-Formyl-5-hydroxy-2-methyl-2,3-dihydrobenzo[*b*]furan-2-carboxaldehyde *N*,*N*-dimethylhydrazone (7d). A solution of 2,5-dihydroxybenzaldehyde(**5a**)(100 mg, 0.72 mmol), silver (II) oxide (269 mg, 1.16 mmol), hydrazone (**4**)(88 mg, 0.8 mmol), magnesium sulfate (0.5 g, 4.15 mmol) in dichloromethane (20 ml) was vigorously stirred for 80 min at ambient temperature. The mixture was filtered and the solids were washed througly with dichloromethane. The solvent was removed under reduced pressure to afford crude **7d** as an oily liquid. Preparative tlc using chloroform as eluant provided pure **7d** (168 mg, 97 %) which solidified on standing for 5-6 days at room temperature; mp 64-65 °C; ir: 3200 (O-H), 1660 (C=O); ^{1}H-nmr: δ 1.63 (s, 3H, 2-Me), 2.84 (s, 6H, NMe_2), 3.22 (d, 1H, $J_{3,3'}$=18, 3-H), 4.04 (d, 1H, $J_{3',3}$=18, 3'-H), 6.70 (s, 1H, CH=N), 6.76 (d, 1H, $J_{6,7}$ =9, 6-H), 6.96 (d, 1H, $J_{7,6}$= 9, 7-H), 10.04 (s, 1H, CHO), 10.68 (s, 1H, OH). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.10; H, 6.70; N, 11.10.

4-Nitro-5-hydroxy-2-methyl-2,3-dihydrobenzo[*b*]furan-2-carboxaldehyde *N*,*N*-dimethylhydrazone (7e). This compound was obtained as its analogue(**7d**)starting from 1,4-dihydroxy-2-nitrobenzene (**5b**) (100 mg, 0.65 mmol), silver (II) oxide (230 mg, 1.00 mmol), hydrazone (**4**) (79 mg, 0.71 mmol). Crude **7e** was purified by preparative tlc using chloroform as eluant to give pure benzofurane (**7e**) (133 mg, 82%) as an orange solid; mp 69-70 °C; ir: 3400-3200 (O-H), 1540, 1460 (NO_2); ^{1}H-nmr: δ 1.64 (s, 3H, 2-Me), 2.84 (s, 6H, NMe_2), 3.45 (d, 1H, $J_{3,3'}$=19, 3-H), 4.21 (d, 1H, $J_{3',3}$ =19, 3'-H), 6.78 (s, 1H, CH=N), 7.00 (d, 1H, $J_{6,7}$=10, 6-H), 7.06 (d, 1H, $J_{7,6}$=10, 7-H), 10.28 (s, 1H, OH). Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.60; H, 5.85; N, 15.68.

7-Bromo-5-hydroxy-4-nitro-2-methyl-2,3-dihydrobenzo[*b*]furan-2-carboxaldehyde *N*,*N*-dimethylhydrazone (7f). This compound was obtained as for **7d,e** starting from 2-bromo-1,4-dihydroxy-5-nitrobenzene (**5f**) (100 mg, 0.43 mmol), silver (II) oxide (159 mg, 0.43 mmol), hydrazone (**4**) (53 mg, 0.47 mmoles). It was purified by preparative tlc (chloroform) to gave pure benzofuran (**7f**) (56 mg, 40%) as an orange solid; mp 100-102°C; ir: 3200 (O-H), 1520, 1450 (NO_2); ^{1}H-nmr: δ 1.68 (s, 3H, 2-Me), 2.84 (s, 6H, NMe_2), 3.52 (d, 1H, $J_{3,3'}$=19, 3-H), 4.52 (d, 1H, $J_{3',3}$= 19), 6.66 (s, 1H, CH=N), 7.22 (s, 1H, 6-H), 10.22 (s, 1H, OH). Anal. Calcd for $C_{12}H_{14}N_3O_4Br$: C, 41.88; H, 4.10; N; 12.21; Br, 23.22. Found: C, 41.70; H, 4.06; N, 11.91; Br, 22.98.

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