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STUDIES ON QUINONES. PART 30. SYNTHESIS OF BENZO[*b*]THIOPHENE-4,7-QUINONES

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The synthesis of a variety of benzo[*b*]thiophene-4,7-quinones (**4a-f**) by oxidative demethylation of the corresponding 4,7-dimethoxybenzo[*b*]thiophenes (**3a-f**) with cerium (IV) ammonium nitrate is reported. Heterocycles (**3a,b**) were prepared by cyclization of the corresponding 2,5-dimethoxy-6-nitrobenzaldehyde (**1a**) and 2,5-dimethoxy-6-nitroacetophenone (**1b**) with methyl thioglycolate.

As part of a program directed towards the synthesis and Diels-Alder reactions of heterocyclic quinones,[1-8] we now report an alternative method for the synthesis of benzo[*b*]thiophene-4,7-quinones. The development of new approaches for these heterocyclic quinones is desirable in view of the antitumoral heteroanalogues of the antitumor drugs, daunomycin and mitoxantrone which contain this structural subunit.[9-12]

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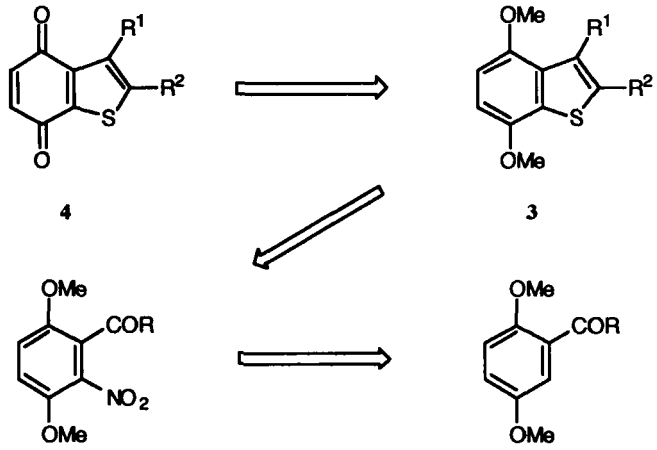
There are some approaches to prepare benzo[*b*]thiophene-4,7-quinones by oxidation of substituted benzo[*b*]thiophenes.[13-17] However, these methods are limited to unsubstituted thiophene ring members in this series and the construction of the benzothiophene precursors requires several steps.

In previous works we have reported a method to prepare thiophene ring substituted benzo[*b*]thiophene-4,7-quinones by reaction of activated 1,4-benzoquinones with methyl thioglycolate followed by cyclization with acetic anhydride-sodium acetate.[1,2] In this regard, our approach provides a valuable precursor of the proper benzo[*b*]thiophene-4,7-quinone which also can serve as general synthon for further elaboration into substituted benzo[*b*]thiophene-4,7-quinones.

The retrosynthetic sequence outlined in Scheme 1 shows our synthetic plan in which the thiophene ring formation is based on the method of Beck[18] which has received little attention.[19] The oxidative demethylation step considered in the sequence is a well-established method to prepare carbo- and heterocyclic quinones by oxidative demethylation of dimethylethers of mono- and policyclic compounds[20] and, as far as we know, there are only one example on its application to the synthesis of the proper benzo[*b*]thiophene-4,7-quinone.[17]

Compound **2a** was prepared by nitration of commercially available 2,5-dimethoxybenzaldehyde (**1a**) with nitric acid-impregnated silica gel using the method previously reported.[21] The

reaction of **2a** with methyl thioglycolate was carried out in DMF solution in the presence of potassium carbonate. After several experiments the heterocycle (**3a**) was obtained in 84% isolated yield, as a sole product (checked by tlc) by heating the reaction mixture at 60°C for two hours (Scheme 2).



2a. R = H
2b. R = Me

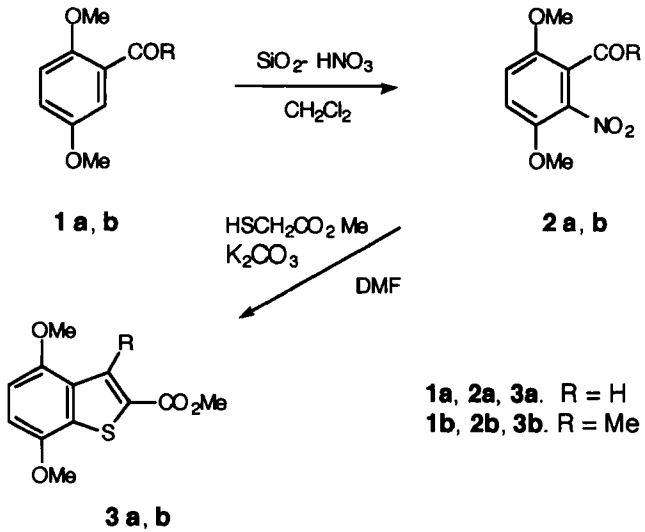
1a. R = H
1b. R = Me

Scheme 1

Cyclization of 4,5-dimethoxy-2-nitrobenzaldehyde reported by Beck[18] proceeds under refluxing condition for 18 h to afford the corresponding benzo[*b*]thiophene in 16% yield. However, the cyclization of compound (**2a**) proceed in high yield, in spite of the steric hindrance on the reactive centers.

The mechanism of the cyclization of *o*-nitrobenzaldehyde derivatives with methyl thioglycolate in basic medium is unknown.

However, it is reasonable to assume that thiophene ring formation involves thiol anion displacement of the activated nitro group followed by base-catalyzed aldol-condensation. By considering this operative reaction course the high yield conversion of **2a** to compound (**3a**) should be favored by the decrease of the steric hindrance involved in the substitution of the nitro group.



Scheme 2

On the basis of the high yield synthesis of benzothiophene (**3a**) by cyclization of compound (**2a**) we investigated the reaction of 2,5-dimethoxy-6-nitroacetophenone (**2b**) with methyl thioglycolate. Ketone (**2b**) was prepared by nitration of 2,5-dimethoxyacetophenone (**1a**) with nitric acid-impregnated silica gel followed by column chromatography separation from its isomer 2,5-

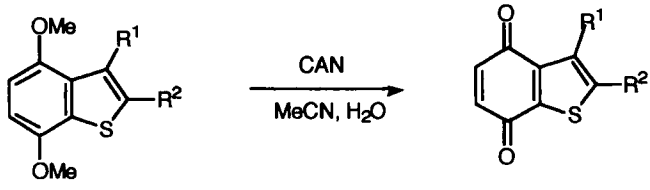
dimethoxy-4-nitroacetophenone. The reaction of **2b** with methyl thioglycolate was conducted under the same conditions as employed to prepare heterocycle (**3a**) to give benzothiophene (**3b**) in 53% yield.

The preparation of benzo[*b*]thiophene-4,7-quinones by oxidative demethylation of 4,7-dimethoxybenzo[*b*]thiophenes was carried out by reaction of compounds (**3a-f**) with cerium (IV) ammonium nitrate (CAN) in acetonitrile-water solution.

Heterocycle **3c** was obtained in 57% yield by reaction of **3a** with LiAlH4 in ethyl ether solution. Hydrolysis of **3a** with potassium hydroxide in methanol at room temperature gave acid (**3d**) and subsequent treatment of **3d** with thionyl chloride and morpholine afforded amide (**3e**). Benzo[*b*]thiophene (**3f**) was obtained in 52% yield by refluxing compound (**3d**) with cuprous oxide in quinoline solution (Table). In all cases the deprotection with CAN proceeded in good yields affording the corresponding quinones (**4a-f**).

In conclusion, a convenient route for the synthesis of benzo[*b*]thiophene-4,7-quinones substituted at the thiophene ring was demonstrated. The main advantage of this approach includes the use of the commercially available starting materials: 2,5-dimethoxybenzaldehyde and 2,5-dimethoxyacetophenone. The facile access to benzo[*b*]thiophene-4,7-quinones by this method and the possibility to extend the anular system through Diels-Alder reactions makes especially atractive the use of these heterocyclic quinones as alternative precursors to the synthesis of thiophene analogues of the antitumor drugs daunomycin and mitoxantrone.

Table. *Synthesis of benzo[b]thiophene-4,7-quinones (**4a-f**) by oxidative demethylation of heterocycles (**3a-f**).*



3a-f **4a-f**

3,4	R^1	R^2	Yield(%)
a	H	CO_2Me	79
b	Me	CO_2Me	42
c	H	CH_2OH	61
d	H	CO_2H	84
e	H	COMorph	90
f	H	H	59

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer for KBr disc and the wave numbers are given in cm^{-1}. ^1H- and ^{13}C-NMR spectra were determined on a Bruker AM-200 in deuteriochloroform. Chemical shifts are reported in δ ppm downfield to TMS, and *J*-values are given in Hertz. Microanalysis and mass spectra, (VB-12-250

spectrometer), were performed in the Instituto de Química General (C.S.I.C), Madrid Spain. Silica gel Merck 60 (70-230 mesh) and DC-Alufolien $60F_{254}$ were normally used for preparative column and analytical TLC, respectively. Preparation of compound (**2a**) was carried out according to previously described procedure.[21]

Methyl 4,7-dimethoxybenzo[*b*]thiophene-2-carboxylate (3a). A solution of 2,5-dimethoxy-6-nitrobenzaldehyde (**2a**) (200 mg, 0.95 mmoles), methyl thioglycolate (110 mg, 0.95 mmol), potassium carbonate (158 mg) in DMF (3.0 ml) was stirred for 2h maintaining a temperature of 60-65°C for 2h. The solution was diluted with water affording compound (**4a**) (201 mg; 84%) as a white pure solid; m.p. 124-125°C (water): Anal. Calcd. for $C_{12}H_{12}O_4S$: C, 57.13; H, 4.80; S, 12.69. Found: C, 56.85; H, 5.03; S, 12.36%, IR: 1710; δ_H: 3.92 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 6.72 (d, 1H, J = 8.5), 6.74 (d, 1H, J = 8.5), 8.21 (s, 1H); δ_C: 52.39, 55.81, 56.01, 104.64, 106.82, 128.01, 131.17, 132.44, 148.47, 150.52, 163.29.

2,5-Dimethoxy-6-nitroacetophenone (2b). A solution of 2,5-dimethoxyacetophenone (**1b**) (472 mg, 2.1 mmol), nitric acid-impregnated silica gel (9g)[20] in CH_2Cl_2 (20 mL) was stirred for 10 h at r. t. The mixture was filtered and the solid was washed with dichloromethane. The solvent was removed by evaporation and the residue was chromatographied on silica gel and eluted with 1:1 ethyl acetate-petroleum ether. From the less polar band 4-nitro-2,5-dimethoxyacetophenone was isolated (181 mg, 31%); mp: 118-120°C

(lit. [21] 122-123°C). From the more polar band compound (**2b**) was obtained (246 mg, 42%); mp.72-73°C (lit.[21] 72-73 °C).

Methyl 4,7-dimethoxy-3-methylbenzo[*b*]thiophene-2-carboxylate (3b). A solution of 2,5-dimethoxy-6-nitroacetophenone (**2b**) (304 mg, 1.35 mmol), methyl thioglycolate (0,15 ml: 1,42 mmol), K_2CO_3 (241 mg, 1.75 mmol) in DMF (3.0 ml) was heated at 60-70 °C for 10 days. Dilution of the mixture precipitated heterocycle (**3b**) (133 mg, 37%) as a white pure solid; m.p.: 151-152° C (water); Anal. Calcd. for $C_{13}H_{14}O_4S$: C, 58.63; H, 5.30; S, 2,02. Found: C, 58.91; H, 5.42; S, 11.98%; IR: 1710; δ_H: 2.98 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 6.80 (d, 1H,J = 8.5), 6.88 (d, 1H, J = 8.5); δ_C : 15.84, 51.95, 55.74, 56.02, 105.20, 106.45, 125.23, 131.20, 131.75, 143.60, 148.26, 152.54, 163.99

4,7-Dimethoxy-2-hydroxymethylbenzo[*b*]thiophene (3c). To a solution of $LiAlH_4$ (1.0 g, 26.4 mmol) in dry ethyl ether (10 ml) was added to a solution of heterocycle (**3a**) (204 mg, 0.81 mmol) in dry ethyl ether (30 ml). The mixture was heated to reflux for 3h under a nitrogen atmosphere. The resulting mixture was acidified with aqueous acetic acid and then extracted with ethyl acetate. The extract was washed with aqueous sodium bicarbonate, water and dried over $MgSO_4$. The solvent was removed by evaporation and the residue was chromatographied on silica gel and eluted with ethyl acetate to afford pure alcohol (**3c**) as a white solid (103 mg, 57%), mp: 132-136°C (benzene); Anal. Calcd. for $C_{11}H_{12}O_3S$: C, 58.92; H, 5.40; S, 14.27. Found: C, 59.10; H, 5.23; S,

14.01%; IR: 3300; δ_H: 1.90 (br s, 1H), 3.96 (s, 3H), 4.00 (s, 3H), 4.97 (s, 2H), 6.72 (s, 2H), 7.43 (s, 1H); δ_C: 55.86, 55.98, 6.93, 104.44, 104.71,118.86, 130.31, 131.66, 144.00, 148.71, 149.33.

4,7-dimethoxybenzo[*b*]thiophene-2-carboxylic acid (3d). A solution of **3a** (159 mg, 0.6 mmol), KOH (125 mg, 0.9 mmoles) in ethanol (10 ml)) was magnetically stirred at room temperature for 30 min. The solution was diluted with 5% hydrochloric acid (15 ml) to afford compound (**3d**) as a yellow solid m.p. 213-215°C (water) ; Anal. Calcd. for $C_{11}H_{10}O_4S$: C,55.46; H, 4.23; S, 13.43. Found: C, 55.66; H, 4.31; S, 13.07%; IR: 3320-2720, 1670; δ_H: 7.10 (d, 1H, J= 8.0), 7.37 (d, 1H, J= 8.0), 8.05 (s, 1H).

4,7-Dimethoxybenzo[*b*]thiophene-2-carboxymorpholide (3e). A solution of **3d** (202 mg; 0,98 mmol), freshly destilled tionyl chloride (300 mg, 2.5 mmol) in benzene (4 ml) was heated to reflux for 3 h. The mixture was evaporated and the residue was chromatographied on silica gel and eluted with chloroform to afford the acid chloride as an stable yellow solid (127 mg, 59%), m.p. 120-121°C; Anal. Calcd. for $C_{11}H_9O_3SCl$: C, 51.56 ; H, 3.54; S, 12.49. Found: C, 51.70; H, 3.51; S,12.21%; IR: 1720, 1740; δ_H: 4.30 (s, 3H), 4.32 (s, 3H), 6.76 (d, 1H, J= 8,5); 6.80 (d, 1H, J= 8.5); 8,41 (s, 1H); δ_C: 55.83; 56.09; 104.95; 108.64; 130.65, 133.46, 134.93, 135.58, 148.19, 151.14, 161.08.

To a solution of the acid chloride (85 mg, 0.33 mmol) in dichloromethane (2 ml) was added dropwise with stirring a solution of dry morpholine (65 mg, 0.74 mmoles) in dichloromethane (5 ml)

and the mixture was left at room temperature for 2h. The mixture was diluted with water and the organic layer was washed with 5% hydrochloric and water. The organic layer was dried over Mg_2SO_4 and evaporated under reduced pressure to afford amide (**3e**)(86 mg, 84%); m.p. 146-147°C (ethanol); Anal. Calcd. for $C_{15}H_{17}NO_4S$: C, 58.62; H, 5.58; N, 4.56; S, 10.41. Found: C, 58.71; H, 5.60; N, 4.54; S, 10.70%; IR: 1620; δ_H: 3.79 (m, 8H), 4.27(s, 3H), 4.31 (s, 3H), 6.69 (d, 1H, J=8.5), 6.73 (d, 1H, J = 8.5) δ_C : 55.79, 56.04, 66.91, 104.82, 105.83, 122.77, 130.87, 135.41, 148.46, 149.94, 163.97.

4,7-Dimethoxybenzo[*b*]thiophene (3f). A solution of acid (**3d**) (197 mg, 0.83 mmol), Cu_2O (406 mg; 0,51 mmol) and quinoline (10 ml) was refluxed for 8 h. The mixture was filtered and the filtrate was diluted with ethyl ether and then washed with 5% aqueous hydrochloric acid. The organic extract was dry over Na_2SO_4 and the solvent removed under reduced pressure. The residue was cromatographied on silica gel (chloroform). Compound (**3d**) was isolated as a white solid m.p. 94-95°C (lit.[16]: m.p. 90.5-92°C); δ_H: 3.93 (s, 3H), 3.96 (s, 3H), 6.68 (s, 2H), 7.37 (d, 1H, J = 5.5), 7.49 (d, 1H, J = 5.5); δ_C: 30.91, 55.84, 55.94, 104.10, 104.43, 121.04, 125.37.

Methyl 4,7-dioxo-4,7-dihydrobenzo[*b*]thiophene-2-carboxylate (4a). Typical Procedure for (4b-f). A solution of CAN (540 mg, 1.00 mmol) in acetonitrile-water (4:1, 5 mL) was added dropwise to **3a** (120 mg, 0.48 mmol) dissolved in acetonitrile

(10 mL). The mixture was kept at room temperature for 10 min., diluted with water (70 ml), and extracted with ethyl acetate (3 x 15 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographied on silica gel (1:1 ethyl acetate-petroleum ether) to afford pure quinone (**4a**) as yellow solid; yield 84 mg, 79%). This quinone was identical in all respect (m.p., tlc, IR and ^{1}H-NMR) with an authentical sample prepared previously in our laboratory.[2]

δ_C: 53.11, 130.62,138.16, 138.21, 140.28, 140.51, 146.33, 161.38, 179.85, 180.56.

Methyl 4,7-dioxo-4,7-dihydro-3-methylbenzo[*b*]thiophene-2-carboxylate (4b). Quinone (**4b**)(25 mg, 42% isolated yield) was prepared from dimethoxybenzothiophene (**3b**) (135 mg; 0.5 mmoles) and CAN (667 mg; 1,2 mmol).The crude product was chromatographied on silica gel (1:1 ethyl acetate-petroleum ether) identical in all respect (tlc, IR and ^{1}H NMR) with an authentical sample prepared previously in our laboratory.[1]

δ_C: 14.34, 52.63, 76.40, 77.04, 77.68, 133.89, 136.92, 137.92, 139.48, 145.78, 147.02, 162.107, 180.26, 182.09.

2-Hydroxymethylenebenzo[*b*]thiophene-4,7-dione (4c). Benzothiophenequinone (**4c**) (52 mg, 61 %) was prepared from benzothiophene (**3c**) (99 mg; 0,44 mmol) and CAN (570 mg; 1,0 mmoles). Crude quinone (**4c**) was purified by column chromatography on silica gel (ethyl acetate); yellow solid m.p. 106-108°C; IR: 3500, 1640; Anal. Calcd. for $C_9H_6O_3S$: C, 55.67; H,

3.12; S, 16.48. Found: C, 55.91; H, 3.18; S, 16.38%; δ_H: 2.14 (t, 1H, J = 5), 4.95 (d, 2H, J=5), 6.77 (d, 1H, J= 10), 6.85 (d, 1H, J= 10): δ_C: 59.03,121.06,137.04,137.84,140.73, 140.80, 156.81, 179.45, 181.24.

4,7-Dioxo-4,7-dihydrobenzo[*b*]thiophene-2-carboxylic acid (4d). Quinone (**4d**) (160 mg, 84 %) was prepared from benzothiophene (**3d**) (215 mg, 0.9 mmol) and CAN (1.3 g, 2.4 mmol). The organic extract was removed to afford crude quinone (**4d**) as orange solid, mp> 300°C. All attempts to purified compound (**4d**) by chromatography were unsuccessful and no correct elemental analysis could be obtained; IR: 3600-3200, 1640; δ_H = 6.90 (d, 1H, J= 10,0), 6.96 (d, 1H, J= 10,0 Hz), 8.23 (s, 1H); MS (EI, 70 eV): m/z = 208 (M^+).

4,7-Dioxo-4,7-dihydrobenzo[*b*]thiophene-2-carboxymorpholide (4e). Quinone (**4e**) was prepared from benzothiophene (**3e**) (32 mg, 0.1 mmoles) and CAN (116 mg, 0.2 mmoles). Removal of the organic extract gave pure quinone as orange crystalls (26 mg, 90 %); m.p. 154-156 °C; Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05; S, 11.54. Found: C, 58.51, H, 4.12; N, 5.10; S, 11,85); δ_H: 3.76 (s, 8H), 6.85 (d, 1H, J = 10), 6.92 (d, 1H, J= 10), 7.60 (s, 1H); δ_C: 66.70, 125.77, 137.85, 138,23, 140.03. 144.09, 144.37, 161.57, 179.57, 180.93.

Benzo[*b*]thiophene-4,7-quinone (4f).

Quinone **4f** was prepared from benzothiophene (**3f**) (89 mg, 0.46 mmoles) and CAN (501 mg, 0.92 mmoles). The crude product

was sublimed at 80-90°C at atmospheric pressure to afford pure **4f** as yellow needles (41 mg, 59%); m.p. 88-89 °C (lit.[23]: 130-131°C); IR: 1680; δ_H: 6.81 (d, 1H, J= 10), 6.88 (d, 1H,J= 10), 7.56 (d, 1H, J= 5.0), 7.70 (d, 1H, J= 5.0); δ_C: 126.14, 133.48, 137.66, 138.12, 141.02, 179.97, 181.42.

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