SYNTHESIS OF THIENOBENZOFURANQUINONE DERIVATIVES BY PHOTOINDUCED AND CAN-MEDIATED 3+2-TYPE CYCLOADDITION REACTIONS

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Abstract- Photoinduced cycloaddition between ethyl 5-hydroxy-3-methyl-4,7-dioxo-4,7-dihydrobenzo[b]thiophene-2-carboxylate (1a) and alkenes is reported to give ethyl 7-methyl-4,8-dioxo-2,3,4,8-tetrahydrothieno[2,3-f]benzofuran-6-carboxylates (2). Cerium(IV) ammonium nitrate (CAN)-mediated cycloaddition of ethyl 5-hydroxy-4,7-dioxo-4,7-dihydrobenzo[b]thiophene-2-carboxylates (1) to alkenes or phenylacetylene, giving ethyl 4,8-dioxo-4,8-dihydrothieno[2,3-f]benzofuran-6-carboxylate (2 or 4) and ethyl 4,5-dioxo-4,5-dihydrothieno[3,2-g]benzofuran-7-carboxylate derivatives (3 or 5), is also reported.

The photoinduced 3+2-type cycloaddition between 2-hydroxy-1,4-naphthoquinones and alkenes has been reported by one of the present authors and shown to give 2,3-dihyronaphtho[2,3-b]furan-4,9-diones in generally good yields.1 We have also reported that when 2-hydroxy-1,4-naphthoquinones were treated with alkenes or phenylacetylene in the presence of CAN,2 naphtho[2,3-b]furan-4,9-dione and naphtho[2,3-b]furan-4,5-dione derivatives could be obtained via the 3+2-type cycloaddition forming a furan ring.3 As part of our continuing study on the synthesis of heterocycle-fused quinone derivatives,4 we have investigated the possibility of the preparation of thienobenzofuranquinone derivatives utilizing these annulation reactions. In this paper, we wish to describe the results of our investigation, which offer a simple method for preparing thieno[2,3-f]benzofuran-4,8-dione (2 and 4) and thieno[3,2-g]benzofuran-4,5-dione derivatives (3 and 5). Thieno[2,3-f]benzofuran-4,8-dione has been prepared by tandem directed metalation,5 and reported to exhibit antitumor activity.6 To the best of our knowledge, however, no other derivatives having thieno[2,3-f]benzofuran-4,8-dione skeleton have been prepared so far, and this is the first construction of the thieno[3,2-g]benzofuran-4,5-dione skeleton.

First, the photoinduced reaction of ethyl 5-hydroxy-3-methyl-4,7-dioxo-4,7-dihydrobenzo[b]thiophene-2-carboxylate (1a) with alkenes was studied. It was found that irradiation of 1a in benzene in the presence
of excess alkenes through a Pyrex filter with a 500W mercury arc led to exclusive formation of 2,3-dihydrothieno[2,3-f]benzofuran-4,8-dione derivatives (2) in fair yields, as illustrated in Scheme 1. The corresponding o-quinone-type products were not obtained in all the present photoreactions, in analogy with the reaction of 2-hydroxy-1,4-naphthoquinone with alkenes.\(^1\)

![Scheme 1.](image)

The CAN-mediated cycloaddition of ethyl 5-hydroxy-4,7-dioxo-4,7-dihydrobenzo[b]thiophene-2-carboxylates (1a and 1b) with alkenes was then carried out. Treatment of 1 with excess alkenes in acetonitrile in the presence of 2 molar amounts of CAN at 0 °C afforded the expected products, 2,3-dihydrothieno[2,3-f]benzofuran-4,8-dione (2) and 2,3-dihydrothieno[3,2-g]benzofuran-4,5-dione derivatives (3), in reasonable combined yields, as illustrated in Scheme 2. Separation of these regioisomers was readily achieved by preparative TLC on silica gel. While each of the p-quinone-type products (2) was more mobile on silica gel chromatography and was isolated as a yellow solid, each of the o-quinone-type products (3) was less mobile and a red solid, as shown by us previously.\(^3\)

![Scheme 2.](image)

Finally, phenylacetylene proved to be usable in this CAN-mediated cycloaddition. Thus, reaction of 1b
with an excess phenylacetylene under similar conditions applied to the reactions using alkenes afforded the corresponding thieno[2,3-f]benzofuran-4,8-dione (4) and thieno[3,2-g]benzofuran-4,5-dione derivatives (5) in the yields indicated in Scheme 3.

In summary, we have demonstrated that the present photoinduced and CAN-mediated 3+2-type cycloaddition reactions provide methodologies for the convenient preparation of thienobenzofuranquinone derivatives, which are hard to be obtained by previous synthetic methods. The ease of operation makes the present procedures attractive.

EXPERIMENTAL
All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer 1600 Series FT IR spectrophotometer as KBr disk. The 1H NMR spectra were determined in CDCl3 using TMS as an internal reference with a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz. J values are given in Hz. The 13C NMR spectra were determined using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz in CDCl3. Low-resolution MS spectral measurements were performed on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). TLC was carried out on a Merck Kieselgel 60 PF254. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. Ethyl 3-methyl(or phenyl)-4,7-dioxo-4,7-dihydrobenzo[b]thiophene-2-carboxylate were prepared by the method reported previously by us.7 All of the other chemicals used in this study were commercially available.

Ethyl 5-Hydroxy-3-methyl-4,7-dioxo-4,7-dihydrobenzo[b]thiophene-2-carboxylates (1a). This compound was prepared according to the procedure for the conversion of methyl 4,7-dioxo-4,7-dihydrobenzo[b]thiophene-2-carboxylate into methyl 5-hydroxy-4,7-dioxo-4,7-dihydrobenzo[b]thiophene-2-carboxylate reported by Ruiz et al.8 Thus, ethyl 3-methyl-4,7-dioxo-4,7-dihydrobenzo[b]thiophene-2-carboxylate7 was treated with acetic anhydride in the presence of boron trifluoride diethyl etherate to give ethyl 4,5,7-triacetxy-3-methylbenzo[b]thiophene-2-carboxylate (73%): a pale-yellow solid; mp 153–156 °C (EtOH); \( \nu_{\text{max}}/\text{cm}^{-1} \) 1777, 1715; \( \delta_H \) 1.40 (3H, t, J 7.3), 2.30 (3H,
Hydrolysis of this triacetate with hydrochloric acid in EtOH, followed by oxidation with FeCl₃ gave 1a (58%): a yellow solid; mp 160–162 °C (decomp) (Et₂O–hexane); \( \text{n}_{\text{max}}/\text{cm}^{-1} \) 3231, 1724, 1674, 1639; \( \delta_t \) 1.40 (3H, t, \( J = 7.3 \)), 2.86 (3H, s), 4.37 (2H, q, \( J = 7.3 \)), 6.23 (1H, s), 7.25–7.3 (3H, m); 7.4–7.55 (3H, m). Anal. Calcd for C₁₂H₁₀O₅S: C, 54.13; H, 3.79; S, 12.04. Found: C, 54.15; H, 3.76; S, 12.03.

**Ethyl 5-Hydroxy-4,7-dioxo-3-phenyl-4,7-dihydrobenzo[\( \text{b} \)]thiophene-2-carboxylate (1b).** This compound was prepared from ethyl 4,7-dioxo-3-phenyl-4,7-dihydrobenzo[\( \text{b} \)]thiophene-2-carboxylate⁷ in a manner similar to that described for the preparation of 1a. Ethyl 4,5,7-triacetoxy-3-phenylbenzo[\( \text{b} \)]thiophene-2-carboxylate (94%): a pale-yellow solid; mp 174–178 °C (EtOH); \( \text{n}_{\text{max}}/\text{cm}^{-1} \) 1774, 1721; \( \delta_t \) 1.11 (3H, t, \( J = 7.3 \)), 1.44 (3H, s), 2.23 (3H, s), 2.43 (3H, s), 4.14 (2H, q, \( J = 7.3 \)), 7.25–7.35 (3H, m), 7.4–7.55 (3H, m). Anal. Calcd for C₂₃H₂₀O₈S: C, 60.52; H, 4.42; S, 7.02. Found: C, 60.29; H, 4.63; S, 6.99. 1b (59%): a yellow solid; 170–175 °C (hexane–Et₂O); \( \text{n}_{\text{max}}/\text{cm}^{-1} \) 3226, 1703, 1680, 1636, 1622; \( \delta_t \) 1.16 (3H, t, \( J = 7.3 \)), 4.19 (2H, q, \( J = 7.3 \)), 6.26 (1H, s), 7.22 (1H, s), 7.25–7.3 (2H, m), 7.4–7.55 (3H, m). Anal. Calcd for C₁₇H₁₂O₅S: C, 62.19; H, 3.68; S, 9.77. Found: C, 62.17; H, 3.61; S, 10.00.

**Ethyl 2,2-Diethyl-7-methyl-4,8-dioxo-2,3,4,8-tetrahydrothieno[2,3-\( \text{f} \)]benzofuran-6-carboxylate (2a).** A solution of hydroxybenzothiophenequinone (1a) (0.37 mmol, 0.10 g) and 2-ethyl-1-butene (3.7 mmol, 0.31 g) in benzene (19 mL) under argon was irradiated through a Pyrex filter with 500W mercury arc for 38 h. After evaporation of the solvent and excess alkene, the residue was purified by preparative TLC on silica gel (hexane–EtOAc 3:1) to give 2a (72 mg, 56%): a yellow solid; mp 77–80 °C (Et₂O–hexane); \( \text{n}_{\text{max}}/\text{cm}^{-1} \) 1721, 1677, 1640, 1615; \( \delta_t \) 0.97 (6H, t, \( J = 7.3 \)), 1.39 (3H, t, \( J = 7.3 \)), 1.7–1.9 (4H, m), 2.85 (3H, s), 2.91 (2H, s), 4.37 (2H, q, \( J = 7.3 \)); MS \( m/z \) 348 (M⁺, 100). Anal. Calcd for C₁₈H₂₀O₅S: C, 62.05; H, 5.79; S, 9.20. Found: C, 62.04; H, 6.00; S, 9.21.

**Ethyl 2,7-Dimethyl-4,8-dioxo-2-phenyl-2,3,4,8-tetrahydrothieno[2,3-\( \text{f} \)]benzofuran-6-carboxylate (2b).** Similar photolysis of quinone (1a) (0.37 mmol, 0.10 g) and \( \text{a} \)-methylstyrene (1.5 mmol, 0.18 g) in benzene (20 mL) as described above for 32 h gave 2b (78 mg, 56%): a yellow solid; mp 133–135°C (Et₂O–hexane); \( \text{n}_{\text{max}}/\text{cm}^{-1} \) 1721, 1677, 1640, 1615; \( \delta_t \) 0.97 (6H, t, \( J = 7.3 \)), 1.39 (3H, t, \( J = 7.3 \)), 1.7–1.9 (4H, m), 2.85 (3H, s), 3.33 (1H, d, \( J = 16.8 \)), 3.39 (1H, d, \( J = 16.8 \)), 4.38 (2H, q, \( J = 7.3 \)), 7.25–7.5 (5H, m); MS \( m/z \) 382 (M⁺, 100). Anal. Calcd for C₂₁H₁₈O₅S: C, 65.95; H, 4.74; S, 8.38. Found: C, 65.85; H, 4.93; S, 8.45.

**Ethyl 2,2,3,7-Tetramethyl-4,8-dioxo-2,3,4,8-tetrahydrothieno[2,3-\( \text{f} \)]benzofuran-6-carboxylate (2c).** Similar photolysis of quinone (1a) (0.37 mmol, 0.10 g) and 2-methyl-2-butene (7.4 mmol, 0.52 g) in benzene (20 mL) as described above for 32 h gave 2c (70 mg, 55%): a yellow solid; mp 138–140 °C (Et₂O–hexane); \( \text{n}_{\text{max}}/\text{cm}^{-1} \) 1721, 1676, 1637, 1606; \( \delta_t \) 1.28 (3H, d, \( J = 7.3 \)), 1.40 (3H, t, \( J = 7.3 \)), 1.47 (3H, s), 1.50 (3H, s), 2.84 (3H, s), 3.21 (1H, q, \( J = 7.3 \)), 4.38 (2H, q, \( J = 7.3 \)); MS \( m/z \) 334 (M⁺, 100). Anal. Calcd for C₁₇H₁₆O₅S: C, 61.06; H, 5.43; S, 9.59. Found: C, 61.11; H, 5.46; S, 9.58.
Ethyl 2,2-Diethyl-7-methyl-4,8-dioxo-2,3,4,8-tetrahydrothieno[2,3-f]benzofuran-6-carboxylate (2a) and Ethyl 2,2-Diethyl-6-methyl-4,5-dioxo-2,3,4,5-dihydrothieno[3,2-g]benzofuran-7-carboxylate (3a). To a stirred solution of hydroxyquinone (1a) (0.37 mmol, 0.10 g) and 2-ethyl-1-butene (3.7 mmol, 0.31 g) in MeCN (17 mL) at 0 °C was added CAN (0.74 mmol, 0.41 g) portionwise. After stirring for 30 min, aqueous saturated NH₄Cl was added. Most of acetonitrile was evaporated and the mixture was extracted with Et₂O twice (15 mL each). The extracts were washed with aqueous saturated NaHCO₃ and then brine, and dried over anhydrous Na₂SO₄. After evaporation of the solvent the residue was purified by preparative TLC on silica gel (AcOEt–hexane 1:3) to give 2a (57 mg, 44%) and 3a (16 mg, 12%).

3a: a red solid; mp 175–178 °C (Et₂O–hexane); \( \nu_{\text{max}}/\text{cm}^{-1} 1717, 1690, 1647; \delta_H 0.97 (6H, t, J 7.3), 1.39 (3H, t, J 7.3), 1.75–1.95 (4H, m), 2.84 (3H, s), 2.86 (2H, s), 4.38 (2H, q, J 7.3); MS \text{m/z} 348 (M⁺, 100). Anal. Calcd for C₁₈H₂₀O₅S: C, 62.05; H, 5.79; S, 9.20. Found: C, 62.24; H, 5.75; S, 9.22.

Ethyl 2,7-Dimethyl-4,8-dioxo-2-phenyl-2,3,4,8-tetrahydrothieno[2,3-f]benzofuran-6-carboxylate (2b) and Ethyl 2,6-Dimethyl-4,5-dioxo-2-phenyl-2,3,4,5-tetrahydrothieno[3,2-g]benzofuran-7-carboxylate (3b). Similar reaction of hydroxyquinone (1a) (0.37 mmol, 0.10 g) with \( \alpha \)-methylstyrene (1.1 mmol, 0.13 g) in MeCN (17 mL) in the presence of CAN (0.74 mmol, 0.41 g) for 25 min gave 2b (50 mg, 35%) and 3b (50 mg, 35%).

3b: a red solid; mp 175–178 °C (Et₂O–hexane); \( \nu_{\text{max}}/\text{cm}^{-1} 1720, 1688, 1651; \delta_H 1.41 (3H, t, J 7.3), 1.89 (3H, s), 2.86 (3H, s), 3.29 (1H, d, J 15.5), 3.35 (1H, d, J 15.5), 4.39 (2H, q, J 7.3), 7.3–7.45 (5H, m); \delta_C 14.22, 14.36, 29.58, 41.06, 61.74, 96.95, 113.61, 124.08, 128.13, 128.76, 130.87, 135.61, 139.79, 143.92, 148.72, 161.65, 162.89, 175.67, 176.52; MS \text{m/z} 382 (M⁺, 100). Anal. Calcd for C₂₁H₁₈O₅S: C, 65.95; H, 4.74; S, 8.38. Found: C, 65.66; H, 5.04; S, 8.18.

Ethyl 2-Methyl-4,8-dioxo-2,7-diphenyl-2,3,4,8-tetrahydrothieno[2,3-f]benzofuran-6-carboxylate (2d) and Ethyl 2-Methyl-4,5-dioxo-2,6-diphenyl-2,3,4,5-tetrahydrothieno[3,2-g]benzofuran-7-carboxylate (3d). Similar reaction of hydroxyquinone (1b) (0.30 mmol, 0.10 g) with \( \alpha \)-methylstyrene (0.91 mmol, 0.11 g) in MeCN (14 mL) in the presence of CAN (0.61 mmol, 0.35 g) for 25 min gave 2d (59 mg, 44%) and 3d (52 mg, 39%).

2d: a yellow solid; mp 74–83 °C (Et₂O–hexane); \( \nu_{\text{max}}/\text{cm}^{-1} 1731, 1682, 1643, 1619; \delta_H 1.14 (3H, t, J 7.3), 1.82 (3H, s), 3.34 (1H, d, J 16.8), 3.41 (1H, d, J 16.8), 4.17 (2H, q, J 7.3), 7.2–7.5 (10H, m); \delta_C 13.76, 29.88, 41.31, 61.77, 94.62, 121.08, 124.08, 127.69, 127.87, 128.27, 128.61, 128.64, 133.28, 134.75, 135.74, 144.41, 147.16, 148.61, 159.66, 160.91, 173.02, 176.92; MS \text{m/z} 444 (M⁺, 100). Anal. Calcd for C₂₆H₂₀O₅S: C, 70.25; H, 4.54; S, 6.96. Found: C, 70.23; H, 4.64; S, 6.97.

3d: a red solid; mp 144–146 °C (Et₂O–hexane); \( \nu_{\text{max}}/\text{cm}^{-1} 1727, 1698, 1658, 1608; \delta_H 1.14 (3H, t, J 7.3), 1.92 (3H, s), 3.28 (1H, J 15.8), 3.37 (1H, d, J 15.8), 4.19 (2H, q, J 7.3), 7.3–7.45 (10H, m); \delta_C 13.76, 29.59, 41.09, 61.78, 97.04, 113.89, 124.10, 127.66, 128.16, 128.39, 128.65, 128.78, 132.67, 132.72, 135.35, 139.90, 143.89, 149.23, 160.87, 162.66, 175.02, 175.54; MS \text{m/z} 444 (M⁺, 100). Anal. Calcd for C₂₆H₂₀O₅S: C, 70.25; H, 4.54; S, 7.21. Found: C, 70.23; H, 4.64; S, 6.97.

Ethyl 4,8-dioxo-2,7-diphenyl-4,8-dihydrothieno[2,3-f]benzofuran-6-carboxylate (4) and Ethyl 4,5-
dioxo-2,6-diphenyl-4,5-dihydrothieno[3,2-g]benzofuran-7-carboxylate (5). Similar reaction of hydroxyquinone (1b) (0.30 mmol, 0.10 g) with ethynylbenzene (0.91 mmol, 93 mg) in MeCN (14 mL) in the presence of CAN (0.61 mmol, 0.35 g) for 25 min gave 4 (40 mg, 31%) and 5 (15 mg, 12%). 4: an orange solid; mp 208–210 °C (Et2O–pentane); $\lambda_{\text{max}}$/cm$^{-1}$ 1731, 1697, 1666; $\delta_1$ 1.15 (3H, t, $J = 7.3$), 4.19 (2H, q, $J = 7.3$), 7.12 (1H, s), 7.25–7.35 (2H, m), 7.4–7.5 (6H, m), 7.75–7.8 (2H, m); $\delta$C 13.79, 61.90, 102.50, 125.28, 127.72, 128.17, 128.30, 128.64, 129.12, 130.23, 131.06, 133.50, 134.49, 137.46, 147.06, 147.72, 151.76, 159.97, 160.81, 169.01, 175.46; MS m/z 428 (M+, 43), 399 (100). Anal. Calcd for C25H16O5S: C, 70.08; H, 3.76; S, 7.48. Found: C, 70.00; H, 3.76; S, 7.35. 5: a purple solid; mp 235–237 °C (Et2O–pentane); $\lambda_{\text{max}}$/cm$^{-1}$ 1736, 1678; $\delta_1$ 1.14 (3H, t, $J = 7.3$), 4.19 (2H, q, $J = 7.3$), 7.06 (1H, s), 7.2–7.3 (2H, m), 7.4–7.55 (6H, m), 7.7–7.8 (2H, m); $\delta$C 13.81, 61.74, 103.62, 123.31, 124.60, 127.76, 128.21, 128.41, 128.53, 129.12, 12.66, 130.30, 132.21, 132.96, 140.88, 149.84, 154.61, 157.92, 160.95, 174.31, and 174.44; MS m/z 428 (M+, 100). Anal. Calcd for C25H16O5S: C, 70.08; H, 3.76; S, 7.48. Found: C, 70.01; H, 4.01; S, 7.26.

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REFERENCES AND NOTES


2. For recent reports on 3+2-type cycloaddition of 1,3-dicarbonyl and related compounds with alkenes mediated by metal catalysts, including CAN, see references cited in the following paper: K. Kobayashi, H. Umakoshi, K. Hayashi, O. Morikawa, and H. Konishi, Chem. Lett., 2004, 33, 1588.


