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CONCISE ROUTE TO 4,5-DIOXO-4,5-DIHYDRONAPHTHO[1,2-*b*]THIOPHENE-2-CARBOXYLATES

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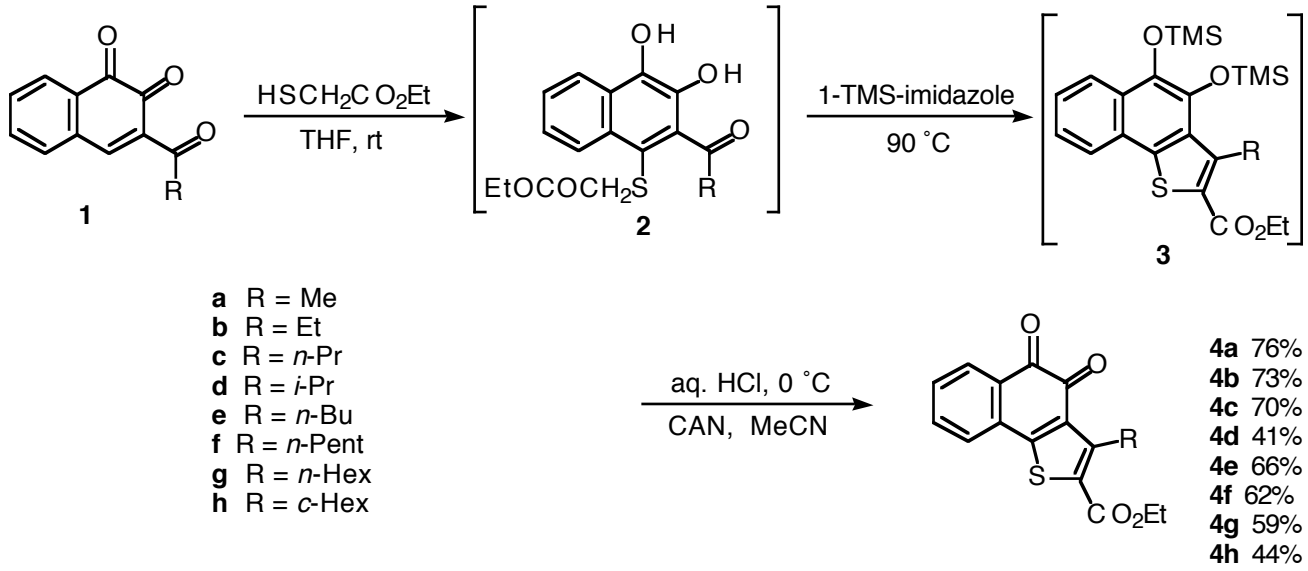
Abstract- Reactions of 3-acyl-1,2-naphthoquinones with ethyl mercaptoacetate followed by protection of the resulting hydroxyl groups and thiophene ring formation using 1-trimethylsilylimidazole, deprotection with hydrochloric acid, and oxidation with cerium(IV) ammonium nitrate (CAN) gave, in one-pot, the title thienonaphthoquinone derivatives in moderate to good yields.

In continuation of our interest in the development of simple and general methods for the preparation of heterocycle-fused quinone derivatives,[1] we recently reported a one-pot synthesis of 4,7-dioxo-4,7-dihydrobenzo[*b*]thiophene-2-carboxylates and 4,9-dioxo-4,9-dihydronaphtho[2,3-*b*]thiophene-2-carboxylates from 2-acyl-1,4-quinones and mercaptoacetates, *via* 1-trimethylsilylimidazole-induced thiophene ring formation.[2a] We also reported a one-pot synthesis of 4,8-dioxo-4,8-dihydrobenz[1,2-*b*:5,4-*b*']dithiophene-2,6-dicarboxylates as an extension of this thiophene ring formation.[2b] In this paper we reports a further attempt to extend this method to a new synthesis of 4,5-dioxo-4,5-dihydronaphtho[1,2-*b*]thiophene-2-carboxylates (**4**) starting from readily available 3-acyl-1,2-naphthoquinones (**1**). Although a number of synthetic methods of naphtho[1,2-*b*]thiophenes have been devised,[3] there are few reports on the synthesis of naphtho[1,2-*b*]thiophene-4,5-dione derivatives,[4] which are of interest from a biological point of view, because some naphtho[2,3-*b*]thiophene-4,9-dione derivatives have been reported to exhibit biological activities.[5]

Our synthesis was conducted as illustrated in the Scheme. Thus, reactions of 3-acyl-1,2-naphthoquinones (**1**) with ethyl mercaptoacetate in THF at room temperature gave 4-sulfenylated hydroquinones (**2**). After removal of THF, protection of hydroxyl groups of these hydroquinones (**2**) and thiophene ring formation were accomplished by treating with 5 molar amounts of 1-trimethylsilylimidazole at 90 ˚C to lead to naphthothiophenes (**3**). After cooling to 0 ˚C, deprotection with hydrochloric acid followed by CAN oxidation gave rise to the expected naphtho[1,2-*b*]thiophene-4,5-diones (**4**). These one-pot syntheses were achieved generally in good yields as depicted in the Scheme. The use of 3-(2-methylpropanoyl)-1,2-



naphthoquinone (**1d**) and 3-cyclohexanecarbonyl-1,2-naphthoquinone (**1h**) somewhat diminished the yields of the corresponding desired products (**4d** and **4h**), probably due to their bulky substituents.

The method appears to be considerably general. Unfortunately, however, 4,5-dioxo-4,5-dihydronaphtho[1,2-*b*]thiophene-2-carboxylates carrying an aromatic substituent at the 3-positions cannot be obtained, because the photoacylation of 1,2-naphthoquinone with aromatic aldehydes, such as benzaldehyde or 4-methylbenzaldehyde, did not gave the desired benzoylated hydroquinones.

In summary, we have shown that 4,5-dioxo-4,5-dihydronaphtho[1,2-*b*]thiophene-2-carboxylates can be obtained in one-pot from readily available starting materials. The method may be of value in heterocyclic quinone synthesis.

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 ^{1}H NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz. *J* values are given in Hz. Low-resolution MS spectra were measured by a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). TLC was carried out on a Merck Kieselgel 60 PF_{254}. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. 3-Acyl-1,2-naphthoquinones (**1**)[6b] were prepared by reductive photoacylation of 1,2-naphthoquinone with aldehydes by the method of Takuwa *et al.*,[6b] followed by oxidation of the resulting 3-acyl-1,2-naphthalenediol[6] with Ag_2O[7] (almost quantitative). Data for new products are as follows. 3-(2-Methylpropanoyl)-1,2-naphthoquinone (**1d**): a red solid; mp 102–106 ˚C (decomp) (benzene–hexane); ν_{max}/cm^{-1} 1708, 1682; δ_H 1.15 (6H, d, *J* 6.9), 3.59 (1H, septet, *J* 6.9), 7.56 (1H, d, *J* 7.6), 7.62 (1H, td, *J*

7.6, 1.3), 7.73 (1H, td, *J* 7.6, 1.3), 8.11 (1H, s), 8.14 (1H, dd, *J* = 7.6 and 1.3 Hz). Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found; C, 73.57; H, 5.30. 3-Hexanoyl-1,2-naphthoquinone (**1f**): a red solid; mp 108–112 ˚C (decomp) (benzene–hexane); ν_{max}/cm^{-1} 1695, 1675; δ_H 0.90 (3H, t, *J* 6.9), 1.3–1.4 (4H, m), 1.55–1.75 (2H, m), 3.00 (2H, t, *J* 7.3), 7.57 (1H, dd, *J* 7.6, 1.3), 7.62 (1H, td, *J* 7.6, 1.3), 7.73 (1H, td, *J* 7.6, 1.3), 8.14 (1H, dd, *J* 7.6, 1.3), 8.16 (1H, s). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found; C, 74.94; H, 6.39. 3-Heptanoyl-1,2-naphthoquinone (**1g**): a red solid; mp 103–108 ˚C (decomp) (benzene–hexane); ν_{max}/cm^{-1} 1682, 1652; δ_H 0.89 (3H, t, *J* 6.6), 1.3–1.45 (6H, m), 1.6–1.7 (2H, m), 3.00 (2H, t, *J* 7.3), 7.57 (1H, d, *J* 7.6), 7.62 (1H, td, *J* 7.6, 1.3), 7.73 (1H, td, *J* 7.6, 1.3), 8.15 (1H, d, *J* 7.6), 8.17 (1H, s). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found; C, 75.51; H, 6.79. (Cyclohexyl)(1,2-dihydroxynaphthalen-3-yl)methanone: 33%; a yellow solid; mp 189–193 ˚C (decomp) (hexane); ν_{max}/cm^{-1} 3481, 1651; δ_H 1.2–1.7 (6H, m), 1.75–2.0 (4H, m), 3.45–3.6 (1H, m), 6.05 (1H, s), 7.36 (1H, ddd, *J* 8.2, 7.9, 1.3), 7.54 (1H, ddd, *J* 8.2, 7.9, 1.3), 7.81 (1H, d, *J* 8.2), 7.98 (1H, s), 8.10 (1H, dd, *J* 8.2, 1.3), 11.90 (1H, s). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found; C, 75.50; H, 6.74. 3-Cyclohexanecarbonyl-1,2-naphthoquinone (**1h**): a red solid; mp 110–113 ˚C (decomp) (benzene–hexane); ν_{max}/cm^{-1} 1682, 1673, 1659; δ_H 0.95–1.45 (6H, m), 1.5–1.95 (4H, m), 3.3–3.4 (1H, m), 7.54 (1H, d, *J* 7.6), 7.61 (1H, td, *J* 7.6, 1.3), 7.72 (1H, td, *J* 7.6, 1.3), 8.08 (1H, s), 8.14 (1H, d, *J* 7.6). Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found; C, 76.07; H, 6.24.

Ethyl 3-Methyl-4,5-dioxo-4,5-dihydronaphtho[1,2-*b*]thiophene-2-carboxylate (4a). Typical Procedure for the Preparation of Thienonaphthoquinones (4). To a stirred solution of 3-acetyl-1,2-naphthoquinone (**1a**) (0.12 g, 0.61 mmol) in THF (1.8 mL) under argon was added ethyl mercaptoacetate (73 mg, 0.61 mmol); the mixture was stirred for 1 h at rt. After removal of THF under reduced pressure, 1-trimethylsilylimidazole (0.43 g, 3.1 mmol) was added to the residue. The mixture was then heated at 90 ˚C for 2 h under stirring. The cooled resulting mixture was dissolved in acetonitrile (2.6 mL) and 10% hydrochloric acid (1.3 mL) was added to this solution at 0 ˚C. After this solution was stirred for 1 h at the same temperature, a solution of CAN (0.67 g, 1.2 mmol) in water (2.6 mL) was added. The orange-red precipitate appeared immediately and it was collected by suction and recrystallized from hexane-$CHCl_3$ to give **4a** (0.46 g, 76%) as red needles; mp 258–261 ˚C; ν_{max}/cm^{-1} 1707, 1665, 1652; δ_H 1.42 (3H, t, *J* 7.3), 2.88 (3H, s), 4.40 (2H, q, *J* 7.3), 7.45–7.55 (1H, m), 7.6–7.7 (2H, m), 8.12 (1H, d, *J* 7.9); MS *m/z* 300 (M^+, 100). Anal. Calcd for $C_{16}H_{12}O_4S$: C, 63.99; H, 4.03; S, 10.68. Found: C, 63.88; H, 4.19; S, 10.46.

Ethyl 3-Ethyl-4,5-dioxo-4,5-dihydronaphtho[1,2-*b*]thiophene-2-carboxylate (4b): red needles; mp 203–205 ˚C (hexane–$CHCl_3$); ν_{max}/cm^{-1} 1712, 1667, 1652; δ_H 1.23 (3H, t, *J* 7.3), 1.42 (3H, t, *J* 7.3), 3.42 (2H, q, *J* 7.3), 4.40 (2H, q, *J* 7.3), 7.45–7.55 (1H, m), 7.6–7.7 (2H, m), 8.12 (1H, d, *J* 7.9); MS *m/z* 314 (M^+, 100). Anal. Calcd for $C_{17}H_{14}O_4S$: C, 64.95; H, 4.49; S, 10.20. Found: C, 64.66; H, 4.39; S, 10.36.

Ethyl 4,5-Dioxo-3-propyl-4,5-dihydronaphtho[1,2-*b*]thiophene-2-carboxylate (4c): orange needles; mp 166–167 ˚C (hexane–$CHCl_3$); ν_{max}/cm^{-1} 1716, 1674, 1655; δ_H 1.03 (3H, t, *J* 7.3), 1.42 (3H, t, *J* 7.3),

1.60 (2H, sextet, *J* 7.3), 3.37 (2H, t, *J* 7.3), 4.39 (2H, q, *J* 7.3), 7.45–7.55 (1H, m), 7.65–7.7 (2H, m), 8.12 (1H, d, *J* 7.9); MS *m/z* 328 (M^+, 100). Anal. Calcd for $C_{18}H_{16}O_4S$: C, 65.84; H, 4.91; S, 9.76. Found: C, 65.59; H, 5.00; S, 9.72.

Ethyl 3-(1-Methylethyl)-4,5-dioxo-4,5-dihydronaphtho[1,2-*b*]thiophene-2-carboxylate (4d): orange needles; mp 194–197 °C (hexane–$CHCl_3$); ν_{max}/cm^{-1} 1716, 1679, 1650; δ_H 1.38 (6H, d, *J* 7.3), 1.42 (3H, t, *J* 7.3), 4.39 (2H, q, *J* 7.3), 4.50 (1H, septet, *J* 7.3), 7.45–7.55 (1H, m), 7.6–7.7 (2H, m), 8.12 (1H, d, *J* 7.3); MS *m/z* 328 (M^+, 31), 282 (100). Anal. Calcd for $C_{18}H_{16}O_4S$: C, 65.84; H, 4.91; S, 9.76. Found: C, 65.74; H, 5.00; S, 9.52.

Ethyl 3-Butyl-4,5-dioxo-4,5-dihydronaphtho[1,2-*b*]thiophene-2-carboxylate (4e): orange needles; mp 169–170 °C (hexane–$CHCl_3$); ν_{max}/cm^{-1} 1713, 1668, 1652; δ_H 0.96 (3H, t, *J* 7.3), 1.42 (3H, t, *J* 7.3), 1.45–1.65 (4H, m), 3.39 (2H, t, *J* 6.9), 4.40 (2H, q, *J* 7.3), 7.45–7.55 (1H, m), 7.6–7.7 (2H, m), 8.12 (1H, d, *J* 7.6); MS *m/z* 342 (M^+, 100). Anal. Calcd for $C_{19}H_{18}O_4S$: C, 66.65; H, 5.30; S, 9.36. Found: C, 66.49; H, 5.31; S, 9.32.

Ethyl 4,5-Dioxo-3-pentyl-4,5-dihydronaphtho[1,2-*b*]thiophene-2-carboxylate (4f): orange needles; mp 150–152 °C (hexane–$CHCl_3$); ν_{max}/cm^{-1} 1712, 1673, 1652; δ_H 0.91 (3H, t, *J* 7.3), 1.35–1.6 (8H, m), 3.38 (3H, t, *J* 7.6), 4.40 (2H, q, *J* 7.3), 7.45–7.55 (1H, m), 7.65–7.7 (2H, m), 8.12 (1H, d, *J* 7.6); MS *m/z* 356 (M^+, 93), 273 (100). Anal. Calcd for $C_{20}H_{20}O_4S$: C, 67.39; H, 5.66; S, 9.00. Found: C, 67.21; H, 5.67; S, 8.91.

Ethyl 3-Hexyl-4,5-dioxo-4,5-dihydronaphtho[1,2-*b*]thiophene-2-carboxylate (4g): orange needles; mp 133–135 °C (hexane–$CHCl_3$); ν_{max}/cm^{-1} 1716, 1674, 1652; δ_H 0.89 (3H, t, *J* 6.9), 1.3-1.65 [11H, m including t (*J* 7.3) at 1.42], 3.38 (2H, t, *J* 7.3), 4.40 (2H, q, *J* 7.3), 7.45–7.55 (1H, m), 7.65–7.7 (2H, m), 8.12 (1H, dd, *J* 7.6, 1.0); MS *m/z* 370 (M^+, 76), 273 (100). Anal. Calcd for $C_{21}H_{22}O_4S$: C, 68.08; H, 5.99; S, 8.66. Found: C, 67.83; H, 6.12; S, 8.62.

Ethyl 3-Cyclohexyl-4,5-dioxo-4,5-dihydronaphtho[1,2-*b*]thiophene-2-carboxylate (4h): orange needles; mp 161–164 °C (hexane–$CHCl_3$); ν_{max}/cm^{-1} 1711, 1674, 1646; δ_H 1.25–1.85 [13H, m including t (*J* 7.3) at 1.43], 2.15–2.2 (1H, m), 4.39 (2H, q, *J* 7.3), 7.45–7.55 (1H, m), 7.65–7.7 (2H, m), 8.11 (1H, d, *J* 7.9); MS *m/z* 368 (M^+, 100). Anal. Calcd for $C_{21}H_{20}O_4S$: C, 68.46; H, 5.47; S, 8.70. Found: C, 68.38; H, 5.67; S, 8.48.

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